532 Rec'd PCT/PTO 22 JUN 2001

FORM PCT 1390
REV. 5/93

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NO.
JOMAA-5 (PCT)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO (if known, see 37 CFR 1.5)
09/868962

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/10274	22 DECEMBER 1999	22 DECEMBER 1998

TITLE OF INVENTION
ORGANO-PHOSPHORUS COMPOUNDS AND THEIR UTILIZATION

APPLICANT(S) FOR DO/EO/US
HASSAN JOMAA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ___ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. X This is an express request to begin national examination procedures (35 U.S.C. 371 (f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2)
   a. X is transmitted herewith (required only if not transmitted by the International Bureau)
   b. ___ has been transmitted by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. X A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ___ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ___ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ___ have been transmitted by the International Bureau.
   c. ___ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ___ have not been made and will not be made.
8. ___ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. X An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ___ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. X An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. X An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. X A **FIRST** preliminary amendment.
    ___ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ___ A substitute specification.
15. ___ A change of power of attorney and/or address letter.
16. X Other items or information:

    PCT/ISA/210 - Int'l. Search Report (English)

Applicant Claims Priority under 35 U.S.C. §119 of German Application No. 198 59 426.7 filed December 22, 1998.
Applicant Claims Priority under 35 U.S.C. §120 of: PCT/EP99/10274 filed December 22, 1999.

APPLICATION NO. (if known, see 37 CFR 1.5) 09/868962	INTERNATIONAL APPLICATION NO. PCT/EP99/10274	ATTORNEY'S DOCKET NO. JOMAA -5 (PCT)

	CALCULATIONS	PTO USE ONLY
X The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO.....**$860.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$690.00**		
Neither international preliminary examination fee paid (37 CFR 1.82) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate		
Total Claims	12 - 20 =	- 0 -	X **$18.00**	$	
Independent Claims	1 - 3 =	- 0 -	X **$80.00**	$	
Multiple dependent claim(s) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction by 1/2 for Small Entity status.				$ 430.00	
SUBTOTAL =				$ 430.00	
Processing fee of **$130.00** for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 430.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				See cover sheet attached to assign $ to be charged to Deposit Acct	
TOTAL FEES ENCLOSED =				$ 430.00	
				Amount to be: refunded	$
				charged	$

X Applicant claims Small Entity status.

a. X A check in the amount of $ 430.00 to cover the above fees is enclosed.

b. ___ Please charge my Deposit Account No. 03-2468 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 03-2468. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
COLLARD & ROE, P.C.
1077 Northern Boulevard
Roslyn, New York 11576-1696
(516) 365-9802

Signature

Edward R. Freedman
Reg. No. 26,048

Express Mail No. **EL 769 393 133 US**
Date of Deposit June 22, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10, on the date indicated above, and is addressed to the Ass't. Commissioner for Patents, Washington, D.C. 20231

Lisa L. Vulpis

09/868962
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: HASSAN JOMAA - 5 (PCT)

PCT NO.: PCT/EP99/10274

FILED: DECEMBER 22, 1999

TITLE: ORGANO-PHOSPHORUS COMPOUNDS AND THEIR UTILIZATION

PRELIMINARY AMENDMENT

BOX PCT
Ass't. Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the initial Office Action, please amend the above-identified application as follows:

IN THE ABSTRACT:

Please add the attached Abstract of the Disclosure on a separate page.

IN THE SPECIFICATION:

On Page 1, above line 1, please insert the following paragraphs:

--CROSS REFERENCE TO RELATED APPLICATIONS

Applicant claims priority under 35 U.S.C. §119 of German Application No. 198 59 426.7 filed December 22, 1998. Applicant also claims priority under 35 U.S.C. §120 of PCT/EP99/10274 filed

December 22, 1999. The international application under PCT article 21(2) was not published in English.--

Also on Page 1, before the second full paragraph, please insert the following paragraphs:

--3-Hydroxy-2-oxo-4-dimethylphosphono- and 3-hydroxy-2-oxo-4-diphenylphosphinyl-1,2-dihydroquinolines and the production thereof are described in Tetrahedron Letters, no. 38, 1972, pages 3979-3982.

N-Substituted alkylaminophosphates are described in Chemical Abstracts, vol. 093, no. 19, 10th November 1989 and Curr. Chemother. Infect. Dis. Proc. Int. Congr. Chemother., 11th; 1980; vol. 1; pages 355-8, in Chemical Abstracts, vol. 105, no. 19, 10th November 1986 and JP 61 106504 A, in US-A-4206 156, in US-A-4 693 742 and in WO99 525 15 A. These compounds are described as suitable for the treatment of bacterial infections. WO 99 525 15 A furthermore describes the use thereof in viral, fungicidal and parasitic infections.--

On Page 3, after formula (IV), insert the following paragraph:

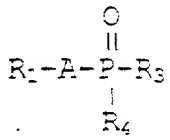
--wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, a (C_{1-3})

alkyl, a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium, or ammonium compounds derived from ethylenediamine or amino acids.--

IN THE CLAIMS:

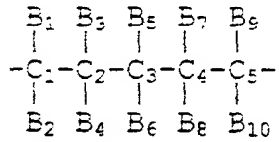
Please cancel claims 1-12 and replace them with claims 13-24 as follows:

--13. Organophosphorus compounds of the general formula (I)



(I)

wherein A is selected from the group which consists of a (C_{1-9}) alkylene residue, which may comprise one or more double bonds and may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, -C-O-C- and -C-N-C-, wherein the carbon atoms of -C-O-C- and -C-N-C- may be substituted with an alkyl having up to 7 carbon atoms or hydroxy groups,
or in which A is of the following formula (II):



(II)

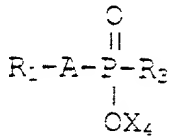
wherein one or more of the carbon atoms selected from the group C_3, C_4, C_5, together with their substituents, may also be absent, and at least one substituent present in the range from B_1 to B_{10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group, wherein both the C_{3-8} cycloalkyl group and the C_{0-9} alkyl group may comprise one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein both the cycloalkyl group and the alkyl group may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, and the remaining substituents B_1 to B_{10} present are selected from the group which consists of hydrogen, hydroxy, halogen, amino groups, C_{1-26} alkyl residues, C_{1-26} alkoxy residues, C_{1-26}-alkoxy-C_{1-26}-alkyl residues or both substituents of a C atom together form an oxo group, wherein each C_{1-26} alkyl residue and each C_{1-26} alkoxy residue may be branched or unbranched and be saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups,
in which R_1 is selected from the group which consists of 5- and 6-membered heterocycles with at least one ring nitrogen atom or a polycyclic carbon with at least one of these heterocycles, wherein at least one of these nitrogen atoms belongs to a hydroxamic acid group or a hydroxamic acid ester group, and may be saturated or unsaturated with one or more double or triple bonds and may thus also be aromatic and may be substituted with hydroxy, halogen, amino, oxo groups and with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be saturated or unsaturated with one or more double or triple bonds and may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, wherein the nitrogen atom of the hydroxamic acid group or hydroxamic acid ester group is substituted with OR_5 and

R_5 is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9} alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9} alkenyl, substituted and unsubstituted C_{1-9} alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue,

in which R_3 and R_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, halogen, OX_3 and OX_4,

wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, a silyl, a cation of an organic and inorganic base, in particular a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
and the pharmaceutically acceptable salts, esters and amides thereof and salts of the esters.

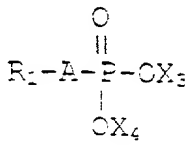
14. Compound according to claim 13, characterised in that the organophosphorus compounds are of the formula (III)



(III)

wherein R_3 is preferably hydrogen, methyl, ethyl, an amide residue and X_4 is selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl.

15. Compound according to claim 13, characterised in that the organophosphorus compounds are of the formula (IV)



(IV)

wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, a (C_{1-3}) alkyl, a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium, or ammonium compounds derived from ethylenediamine or amino acids.

16. Compound according to claim 13, characterised in that X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl.

17. Compound according to claim 13, characterised in that A is selected from the group which consists of alkylene, alkenylene, hydroxyalkylene and oxoalkylene.

18. Compound according to claim 17, characterised in that A is selected such that three atoms are present between the nitrogen atom of the heterocyclic group and the phosphorus atom, wherein A is preferably a methylene, hydroxymethylene, ethylene, ethenylene or hydroxyethylene.

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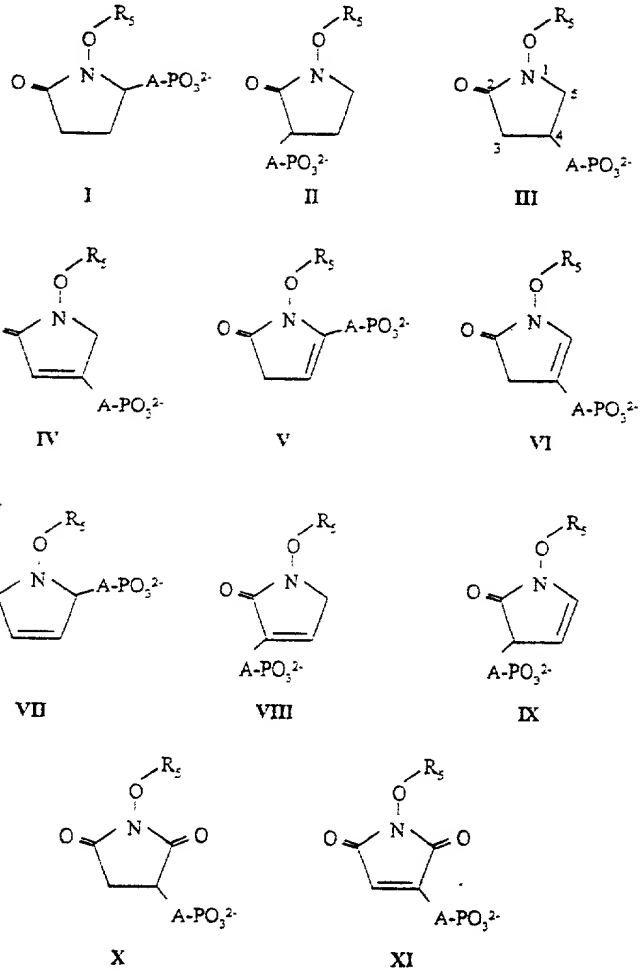
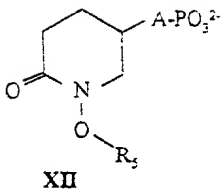
19. Compound according to claim 13, characterised in that the compound is selected from the group of compounds which consists of





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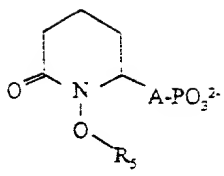

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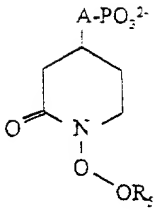

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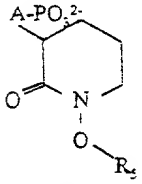

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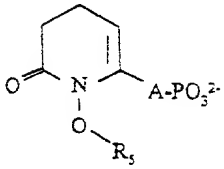

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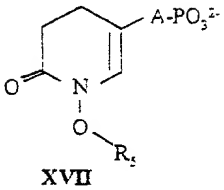

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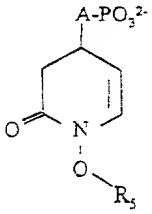

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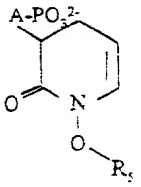

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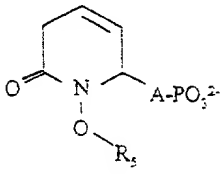

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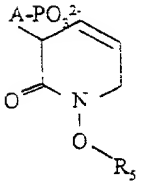

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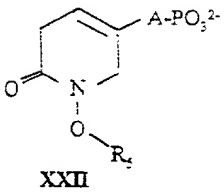

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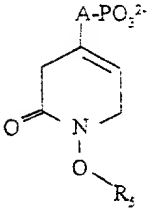

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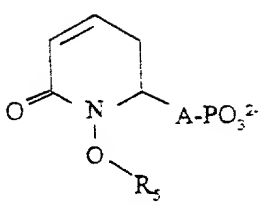

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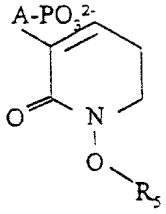

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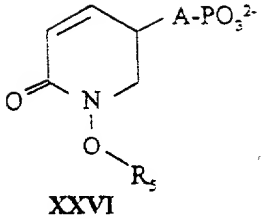

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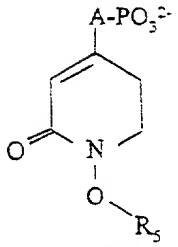

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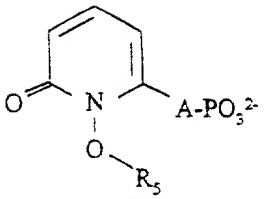

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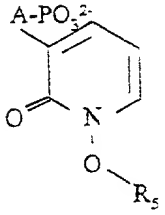

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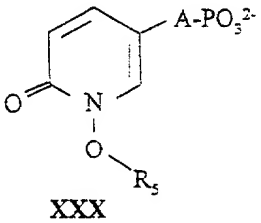

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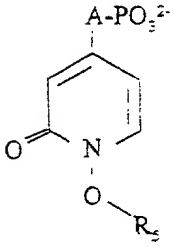

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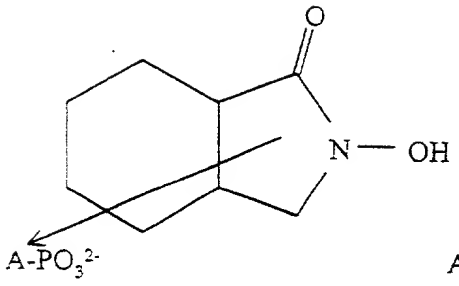

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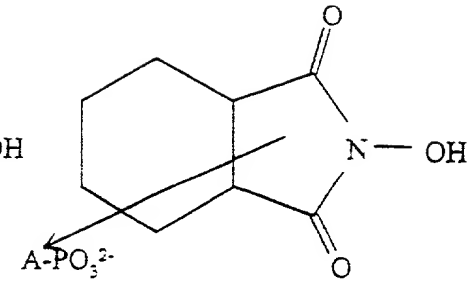

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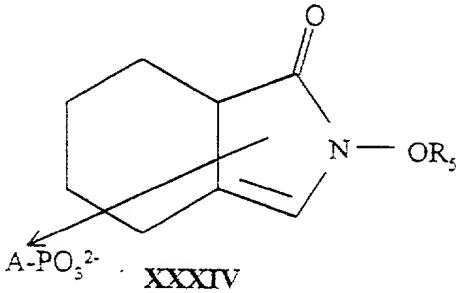

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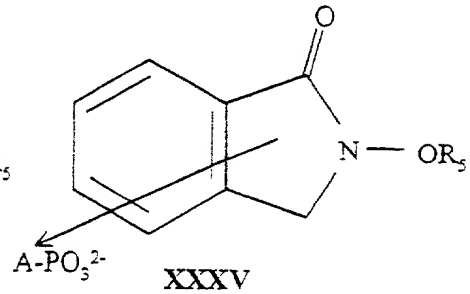
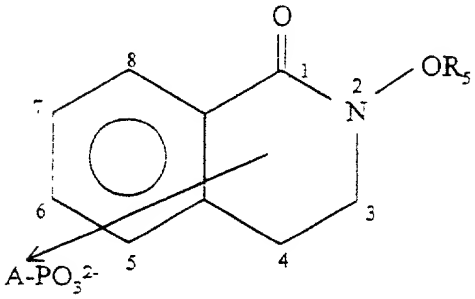


XXXV



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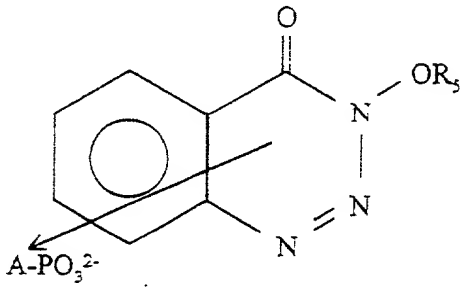

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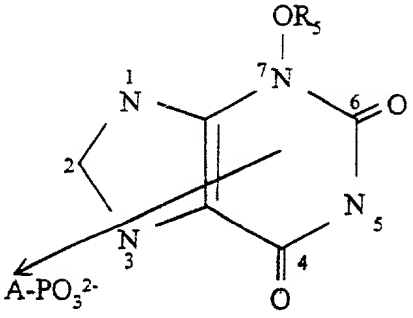

XXXVIII

and the corresponding phosphinic acid and phosphinoyl derivatives, wherein R_5 is defined as in claim 13.

20. Use of a compound according to claim 13 as a fungicide, bactericide or herbicide in plants.

21. Use according to claim 13 for the treatment of infections caused by bacteria, viruses, fungi or uni- or multicellular parasites.

22. Use according to claim 21 for the prevention and treatment of infections caused by unicellular parasites, namely the causative organisms of malaria, sleeping sickness, Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

23. Pharmaceutical preparation for the therapeutic and prophylactic treatment of infectious processes, characterised in that the preparation contains an active content of at least one organophosphorus compound according to claim 13 together with a pharmaceutically acceptable excipient.

24. Pharmaceutical preparation according to claim 23, characterised in that the preparation contains another pharmaceutical active substance. --

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REMARKS

By this Preliminary Amendment, the application has been amended to conform with U.S. practice, the cross-reference to related applications has been inserted on page 1, claims 1-12 have been canceled and replaced with new claims 13-24 and an Abstract has been provided. No new matter has been introduced. Entry of this amendment is respectfully requested.

Respectfully submitted,
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Date of Deposit June 22, 2001

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Lisa L. Vulpis

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ABSTRACT OF THE DISCLOSURE

The invention relates to organo-phosphorus compounds of formula (I), wherein A is selected from the group consisting of a (C_{1-9}) alkylene radical, -C-O-C- and -C-N-C- or A corresponds to formula (II), wherein one or more carbon atoms selected from the group consisting of C_3, C_4, C_5 and their substituents can also be absent and at least one of the substituents of B_1 to B_{10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group in which R_1 is selected from the group consisting of five and six membered heterocycles having at least one nitrogen atom in the ring or polycyclic carbon atoms containing one of said heterocycles, wherein at least one of said nitrogen atoms belongs to a hydroxamic acid group or a hydroxamic acid ester group. The invention also relates to the utilization of the above-mentioned compounds in the therapeutic and prophylatic treatment of infections in human beings and animals caused by virus, bacteria, fungi and parasites and as fungicides, bactericides and herbicides in plants.

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Organophosphorus compounds and use thereof

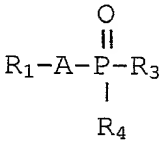
This invention relates to organophosphorus compounds, to the salts, esters and amides thereof and to the use thereof for the therapeutic and prophylactic treatment of infections in humans and animals which are caused by viruses, bacteria, fungi and parasites, to the use thereof as a fungicide, bactericide and herbicide in plants. According to the invention, the organophosphorus compounds comprise phosphinoyl derivatives, phosphinic acid derivatives and phosphonic acid derivatives.

In order to widen the range of options for treating humans and animals, there is an urgent requirement to provide agents which are not only highly active but, unlike other pharmaceutical preparations, also exhibit reduced side-effects and thus constitute a reduced risk to human health.

The object of the present invention is accordingly to provide a substance which is universally usable in infections by viruses, bacteria, fungi and parasites in humans and animals and which meets the above-stated requirements.

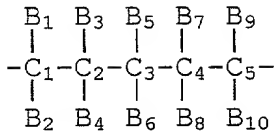
This object is utterly surprisingly achieved by the group of substances defined in claim 1. This group of substances exhibits antiinfective action against viruses, bacteria, fungi and uni- and multicellular parasites. Fungicidal, bactericidal and herbicidal action has also been observed in plants.

The organophosphorus compounds according to the invention are of the general formula (I):



(I)

wherein A is selected from the group which consists of a (C_{1-9}) alkylene residue, which may comprise one or more double bonds and may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, -C-O-C- and -C-N-C-, wherein the carbon atoms of -C-O-C- and -C-N-C- may be substituted with an alkyl having up to 7 carbon atoms or hydroxy groups,
or in which A is of the following formula (II):



(II)

wherein one or more of the carbon atoms selected from the group C_3, C_4, C_5, together with their substituents, may also be absent, and at least one substituent present in the range from B_1 to B_{10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group, wherein both the C_{3-8} cycloalkyl group and the C_{0-9} alkyl group may comprise one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein both the cycloalkyl group and the alkyl group may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, and the remaining substituents B_1 to B_{10} present are selected from the group which consists of hydrogen, hydroxy, halogen, amino groups, C_{1-26} alkyl residues, C_{1-26} alkoxy residues, C_{1-26}-alkoxy-C_{1-26}-alkyl residues or both substituents of a C atom together form an oxo group, wherein each C_{1-26} alkyl residue and each C_{1-26} alkoxy residue may be branched or unbranched and be saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups,

in which R_1 is selected from the group which consists of 5- and 6-membered heterocycles with at least one ring nitrogen atom or a polycyclic carbon with at least one of these heterocycles, wherein at least one of these nitrogen atoms belongs to a hydroxamic acid group or a hydroxamic acid ester group, and may be saturated or unsaturated with one or more double or triple bonds and may thus also be aromatic and may be substituted with hydroxy, halogen, amino, oxo groups and with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be saturated or unsaturated with one or more double or triple bonds and may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, wherein the nitrogen atom of the hydroxamic acid group or hydroxamic acid ester group is substituted with OR_5 and

R_5 is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9} alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9} alkenyl, substituted and unsubstituted C_{1-9} alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue,

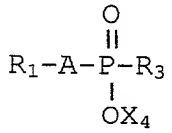
in which R_3 and R_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, hydroxy-C_{1-26}-alkyl, substituted and

unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, halogen, OX_3 and OX_4,

wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, a silyl, a cation of an organic and inorganic base, in particular a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
and the pharmaceutically acceptable salts, esters and amides thereof and salts of the esters.

If two or more heteroatoms are present in the heterocycle R_1, oxygen and sulfur atoms may be present.

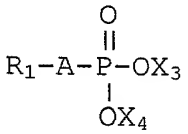
The organophosphorus compounds are preferably of the formula (III)



(III)

wherein R_3 is preferably hydrogen, methyl, ethyl, an amide residue or OX_3 and X_4 is selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl, wherein X_3 is defined as above

and particularly preferably of the formula (IV)



(IV)

X_3 and X_4 are preferably a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium or ammonium compounds derived from ethylenediamine or amino acids. In other words, the salt compounds of the organophosphorus compounds are

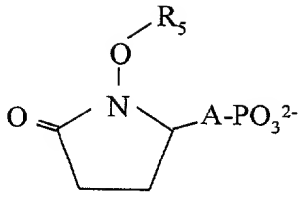
formed with organic or inorganic bases (for example sodium salt, potassium salt, calcium salt, aluminium salt, ammonium salt, magnesium salt, triethylamine salt, ethanolamine salt, dicyclohexylamine salt, ethylenediamine salt, N,N'-dibenzylethylenediamine salts) as well as salts with amino acids (for example arginine salt, aspartic acid salt, glutamic acid salt etc.) and the like.

X_3 and X_4 are particularly preferably identical or different and are selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl.

A is preferably selected such that a three-membered linking chain is formed between the phosphorus atom and the nitrogen atom of the heterocycle. A is for example advantageously a methylene, hydroxymethylene, ethylene, ethenylene, hydroxyethylene and may in particular also be substituted with an oxo group.

The carbon chain of A with the formula (II) preferably also links, together with the atoms of the heterocycle, the nitrogen and phosphorus atom via three atoms. If the carbon atom arranged in α position relative to the nitrogen or phosphorus atom is substituted with an oxo group in the linking chain, linking chains having four carbon atoms are also preferred. If both an oxo group is in α position relative to the nitrogen atom and another oxo group is in α position relative to the phosphorus atom in this linking chain, a linking chain with five carbon atoms is also preferred. If the carbon atom arranged in α position relative to the phosphorus atom is substituted with a hydroxy group, linking chains having four carbon atoms are preferred. In this case, methylene groups are also preferred for R_3 and R_4.

Very particularly preferred groups of compounds are listed below:



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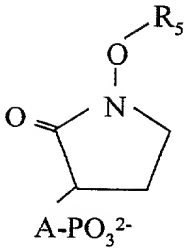

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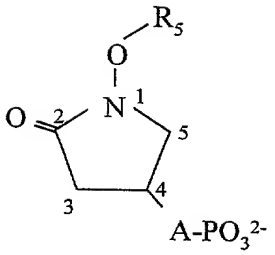

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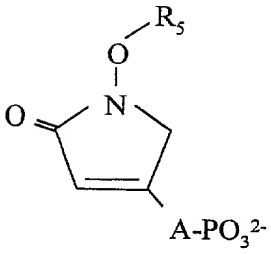

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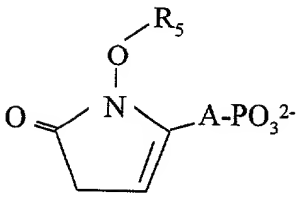

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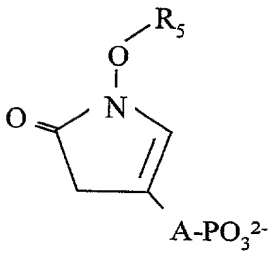

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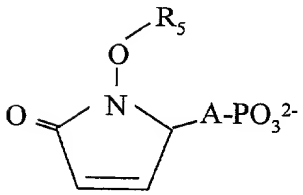

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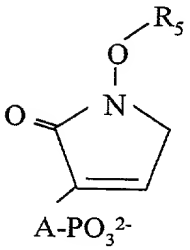

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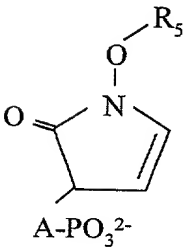

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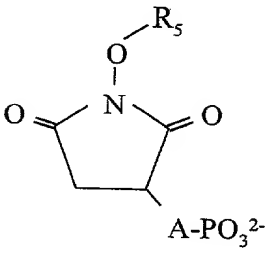

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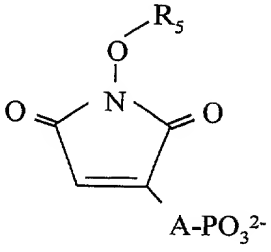

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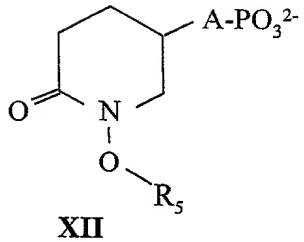

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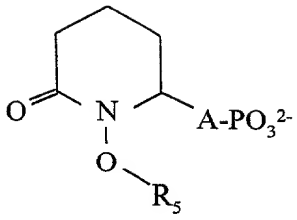

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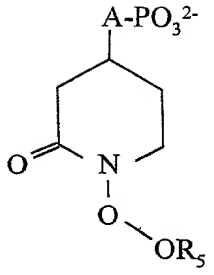

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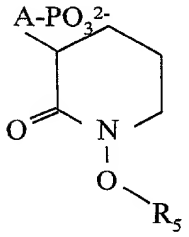

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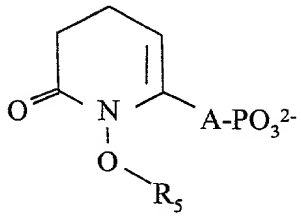

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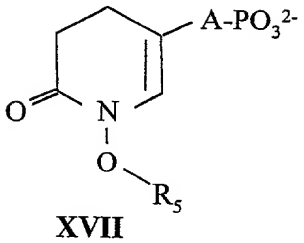

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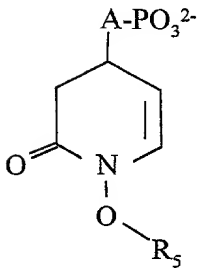

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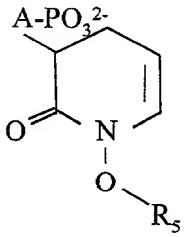

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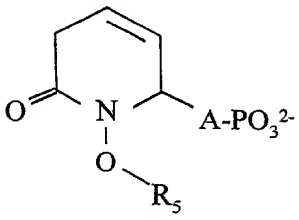

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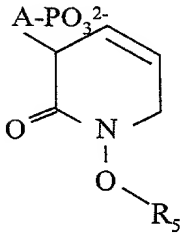

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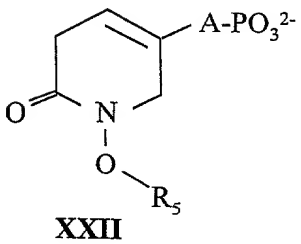

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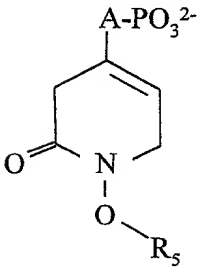

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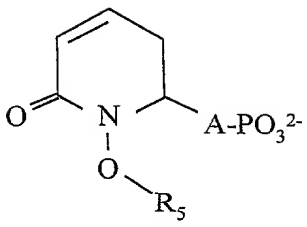

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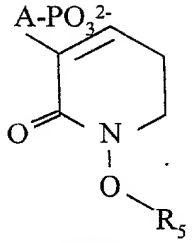

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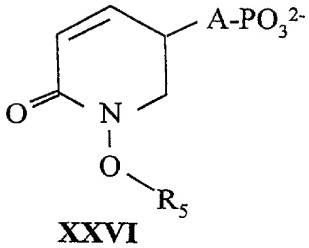

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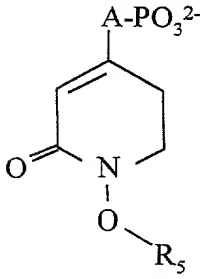

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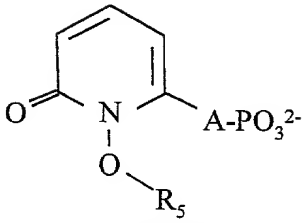

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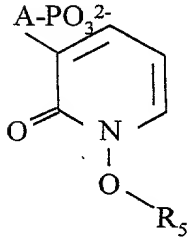

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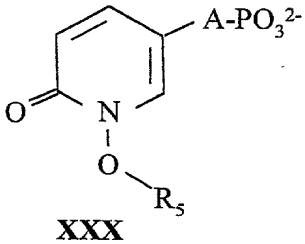

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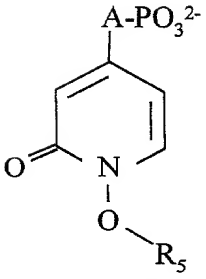

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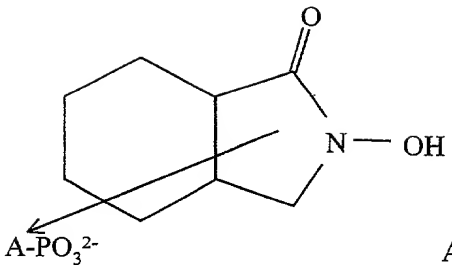

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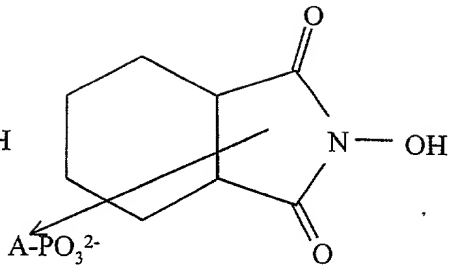

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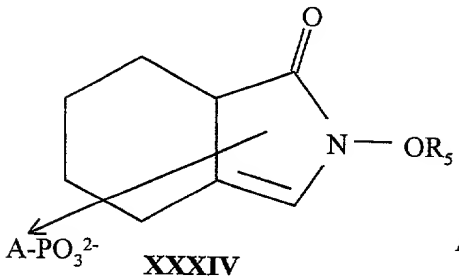

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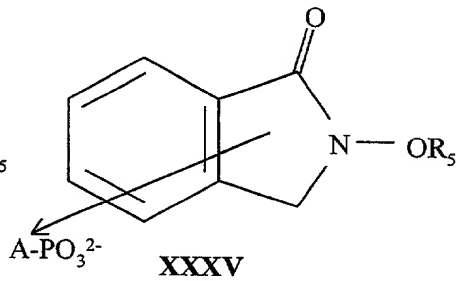

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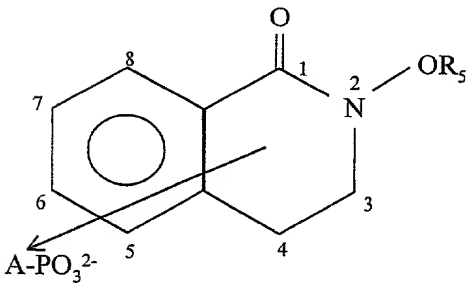

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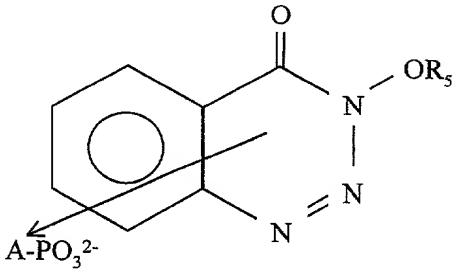

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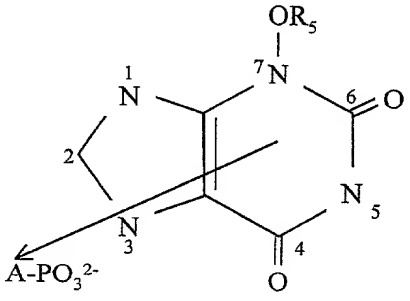

XXXVIII

and the corresponding phosphinic acid and phosphinoyl derivatives.

Special features of the above definitions and suitable examples thereof are given below:

"Acyl" is a substituent which originates from an acid, such as from an organic carboxylic acid, carbonic acid, carbamic acid or the thio acid or imidic acid corresponding to the above individual acids, or from an organic sulfonic acid, wherein these acids in each case comprise aliphatic, aromatic and/or heterocyclic groups in the molecule together with carbamoyl or carbamimidoyl.

Suitable examples of these acyl groups are given below.
Aliphatic acyl groups are defined as acyl residues originating from an aliphatic acid and include the following:
alkanoyl (for example formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl etc.); alkenoyl (for example acryloyl, methacryloyl, crotonoyl etc.); alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl etc.); alkanesulfonyl (for example mesyl, ethanesulfonyl, propanesulfonyl etc.); alkoxycarbonyl (for example methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl etc.); alkylcarbamoyl (for example methylcarbamoyl etc.); (N-alkyl)thiocarbamoyl (for example (N-methyl)thiocarbamoyl etc.); alkylcarbamimidoyl (for example methylcarbamimidoyl etc.); oxalo; alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl etc.).

In the above examples of aliphatic acyl groups, the aliphatic hydrocarbon moiety, in particular the alkyl group or alkane residue, may optionally have one or more suitable substituents, such as amino, halogen (for example fluorine, chlorine, bromine etc.), hydroxy, hydroxyimino, carboxy, alkoxy (for example methoxy, ethoxy, propoxy etc.), alkoxycarbonyl, acylamino (for example benzyloxycarbonylamino etc.), acyloxy (for example acetoxy, benzoyloxy etc.) and the like; preferred aliphatic acyl residues with such substituents which may be mentioned are, for example, alkanoyls substituted with amino, carboxy, amino and carboxy, halogen, acylamino or the like.

Aromatic acyl residues are defined as those acyl residues which originate from an acid with a substituted or unsubstituted aryl group, wherein the aryl group may comprise phenyl, toluyl, xylyl, naphthyl and the like; suitable examples are stated below:
aroyl (for example benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl etc.); aralkanoyl (for example phenylacetyl etc.); aralkenoyl (for example cinnamoyl etc.); aryloxyalkanoyl (for example phenoxyacetyl etc.); arylthioalkanoyl (for example phenylthioacetyl etc.);

arylaminoalkanoyl (for example N-phenylglycyl, etc.); arenesulfonyl (for example benzenesulfonyl, tosyl or toluenesulfonyl, naphthalenesulfonyl etc.); aryloxycarbonyl (for example phenoxycarbonyl, naphthyloxycarbonyl etc.); aralkoxycarbonyl (for example benzyloxycarbonyl etc.); arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl etc.); arylglyoxyloyl (for example phenylglyoxyloyl etc.).

In the above-stated examples of aromatic acyl residues, the aromatic hydrocarbon moiety (in particular the aryl residue) and/or the aliphatic hydrocarbon moiety (in particular the alkane residue) may optionally have one or more suitable substituents, such as those which have already been stated as suitable substituents for the alkyl group or the alkane residue. Examples of preferred aromatic acyl residues with specific substituents which may in particular be mentioned are aroyl substituted with halogen and hydroxy or with halogen and acyloxy, and aralkanoyl substituted with hydroxy, hydroxyimino, dihaloalkanoyloxyimino, together with arylthiocarbamoyl (for example phenylthiocarbamoyl etc.); arylcarbamimidoyl (for example phenylcarbamimidoyl etc.).

A heterocyclic acyl residue is taken to mean an acyl residue which originates from an acid with a heterocyclic group; such residues include:

heterocyclic carbonyl, in which the heterocyclic residue is an aromatic or aliphatic 5- to 6-membered heterocycle with at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenyl, furoyl, pyrrolecarbonyl, nicotinyl etc.);

heterocycle-alkanoyl, in which the heterocyclic residue is 5- to 6-membered and comprises at least one heteroatom from the group nitrogen, oxygen and sulfur (for example thiophenylacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl etc.) and the like.

In the above Examples of heterocyclic acyl residues, the heterocycle and/or the aliphatic hydrocarbon moiety may optionally comprise one or more suitable substituents, such as the same as were stated to be suitable for alkyl and alkane groups.

"Alkyl" is a linear or branched alkyl residue, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and the like.

"Hydroxyalkyl" is a linear or branched alkyl residue which comprises at least one hydroxyl group, preferably one or two hydroxyl groups.

"Alkenyl" includes linear or branched alkenyl groups, such as for example vinyl, propenyl (for example 1-propenyl, 2-propenyl), 1-methylpropenyl, 2-methylpropenyl, butenyl, 2-ethylpropenyl, pentenyl, hexenyl.

"Alkynyl" includes linear or branched alkynyl groups.

Cycloalkyl preferably denotes an optionally substituted C_{3-8} cycloalkyl; possible substituents are inter alia alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

Aryl is an aromatic hydrocarbon residue, such as phenyl, naphthyl etc., which may optionally comprise one or more suitable substituents, such as alkyl, alkenyl, alkynyl, alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

"Aralkyl" includes mono-, di-, triphenylalkyls such as benzoyl, phenethyl, benzhydryl, trityl and the like, wherein the aromatic moiety may optionally comprise one or more suitable substituents, such as alkoxy (for example methoxy, ethoxy etc.), halogen (for example fluorine, chlorine, bromine etc.), nitro and the like.

The residues X_3 and X_4 may preferably be selected such that esters are formed on the phosphino group or phosphono group. Suitable examples of such esters according to the formulae (I), (III) and (IV) include suitable mono- and diesters, and preferred examples of such esters include alkyl esters (for example hexadecanyl ester, octadecanyl ester etc.); aralkyl esters (benzyl ester, phenethyl ester, benzhydryl ester, trityl ester etc.); aryl esters (for example phenyl ester, tolyl ester, naphthyl ester etc.); aroylalkyl esters (for example phenacyl ester etc.); and silyl esters (for example of trialkylhalosilyl, dialkyldihalosilyl, alkyltrihalosilyl, dialkylarylhalosilyl, trialkoxyhalosilyl, dialkylaralkylhalosilyl, dialkoxydihalosilyl, trialkoxyhalosilyl etc.) and the like.

In the above esters, the alkane and/or arene moiety may optionally comprise at least one suitable substituent, such as halogen, alkoxy, hydroxy, nitro or the like.

The compounds used according to the invention according to the formulae (I), (III) and (IV) may be present in the protonated form thereof as an ammonium salt of organic or inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, acetic acid, lactic acid, maleic acid, fumaric acid, oxalic acid, tartaric acid, benzoic acid etc..

The compounds used according to the invention of the formulae (I), (III) and (IV) permit, for example for groups R_1, R_3, R_4, X_3, X_4 or A which contain double bonds or are chiral, the occurrence of steric isomers. The use according to the invention of the compounds includes all steric isomers, both as pure substances and in the form of mixtures.

The organophosphorus compounds are suitable for the therapeutic and prophylactic treatment of infections in humans and animals caused by viruses, bacteria, uni- and multicellular parasites and fungi.

The compounds are active against unicellular parasites (protozoa), in particular against the causative organisms of malaria and sleeping sickness and of Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

They are accordingly in particular suitable for the prophylactic treatment of malaria and of sleeping sickness and of Chagas' disease, of toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

The active substances according to the invention may in particular be used against the following bacteria:
bacteria of the family Propionibacteriaceae, in particular of the genus Propionibacterium, in particular the species Propionibacterium acnes, bacteria of the family Actinomycetaceae, in particular of the genus Actinomyces, bacteria of the genus Cornynebacterium, in particular the species Corynebacterium diphtheriae and Corynebacterium pseudotuberculosis, bacteria of the family Mycobacteriaceae, of the genus Mycobacterium, in particular the species Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium avium, bacteria of the family Chlamydiaceae, in particular the species Chlamydia trachomatis and Chlamydia psittaci, bacteria of the genus Listeria, in particular the species Listeria monocytogenes, bacteria of the species Erysipelthrix rhusiopathiae, bacteria of the genus Clostridium, bacteria of the genus Yersinia, the species Yersinia pestis, Yersinia pseudotuberculosis, Yersinia enterocolitica and Yersinia ruckeri, bacteria of the family Mycoplasmataceae, of the genera Mycoplasma and Ureaplasma, in particular the species Mycoplasma pneumoniae, bacteria of the genus Brucella, bacteria of the genus Bordetella, bacteria of the family Neisseriaceae, in particular of the genera Neisseria and Moraxella, in particular the species Neisseria meningitides, Neisseria gonorrhoeae and Moraxella bovis,

bacteria of the family Vibrionaceae, in particular of the genera Vibrio, Aeromonas, Plesiomonas and Photobacterium, in particular the species Vibrio cholerae, Vibrio anguillarum and Aeromonas salmonicidas, bacteria of the genus Campylobacter, in particular the species Campylobacter jejuni, Campylobacter coli and Campylobacter fetus, bacteria of the genus Helicobacter, in particular the species Helicobacter pylori, bacteria of the families Spirochaetaceae and Leptospiraceae, in particular of the genera Treponema, Borrelia and Leptospira, in particular Borrelia burgdorferi, bacteria of the genus Actinobacillus, bacteria of the family Legionellaceae, of the genus Legionella, bacteria of the family Rickettsiaceae and family Bartonellaceae, bacteria of the genera Nocardia and Rhodococcus, bacteria of the genus Dermatophilus, bacteria of the family Pseudomonadaceae, in particular of the genera Pseudomonas and Xanthomonas, bacteria of the family Enterobacteriaceae, in particular of the genera Escherichia, Klebsiella, Proteus, Providencia, Salmonella, Serratia and Shigella, bacteria of the family Pasteurellaceae, in particular of the genus Haemophilus, bacteria of the family Micrococcaceae, in particular of the genera Micrococcus and Staphylococcus, bacteria of the family Streptococcaceae, in particular of the genera Streptococcus and Enterococcus and bacteria of the family Bacillaceae, in particular of the genera Bacillus and Clostridium.

The organophosphorus compounds and the derivatives thereof are consequently suitable for treating diphtheria, acne vulgaris, listerioses, swine erysipelas in animals, gas gangrene in humans and animals, malignant oedema in humans and animals, tuberculosis in humans and animals, leprosy and further mycobacterioses in humans and animals, paratuberculosis in animals, plague, mesenterial lymphadenitis and pseudotuberculosis in humans and animals, cholera, legionnaires' disease, borreliosis in humans and animals, leptospiroses in humans and animals, syphilis, Campylobacter enteritis infections in humans and animals, Moraxella keratoconjunctivitis and serositis in animals, brucellosis of animals and humans, anthrax in humans and animals, actinomycosis in humans and animals, streptotrichoses, psittacosis/ortnithosis in animals, Q fever, ehrlichiosis.

Use is furthermore in particular preferred in the eradication of Helicobacter in ulcers of the gastrointestinal tract.

Combinations with another antibiotic may also be used to treat the above-stated diseases. Isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, protionamide and dapsone are in particular suitable for combination preparations with other antiinfective agents for the treatment of tuberculosis.

The active substances according to the invention are furthermore in particular usable in infections with the following viruses:

Parvoviridae: parvoviruses, dependoviruses, densoviruses, Adenoviridae: adenoviruses, mastadenoviruses, aviadenoviruses, Papovaviridae: papovaviruses, in particular papillomaviruses ("wart" viruses), polyomaviruses, in particular JC virus, BK virus and miopapovaviruses,
Herpesviridae: all herpesviruses, in particular herpes simplex viruses, varicella-zoster viruses, human cytomegalovirus, Epstein-Barr viruses, all human herpesviruses, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8, Poxiviridae: poxviruses, orthopoxviruses, parapoxviruses, molluscum contagiosum virus, aviviruses, capriviruses, leporipoxviruses, all primarily hepatotropic viruses, hepatitisviruses: hepatitis A viruses, hepatitis B viruses, hepatitis C viruses, hepatitis D viruses, hepatitis E viruses, hepatitis F viruses, hepatitis G viruses, hepadnaviruses: all hepatitisviruses, hepatitis B virus, hepatitis D viruses, Picornaviridae: picornaviruses, all enteroviruses, all polioviruses, all coxsackie-viruses, all echoviruses, all rhinoviruses, hepatitis A virus, aphthoviruses, Calciviridae: hepatitis E viruses, Reoviridae: reoviruses, orbiviruses, rotaviruses, Togaviridae: togaviruses, alphaviruses, rubiviruses, pestiviruses, rubellavirus, Flaviviridae: flaviviruses, FSME virus, hepatitis C virus, Orthomyxoviridae: all influenza viruses, Paramyxoviridae: paramyxoviruses, morbillivirus, pneumovirus, measles virus, mumps virus, Rhabdoviridae: rhabdoviruses, rabies virus, lyssavirus, vascular stomatitisvirus, Coronaviridae: coronaviruses, Bunyaviridae: bunyaviruses, nairovirus, phlebovirus, uukuvirus, hantavirus, hantaan virus, Arenaviridae: arenaviruses, lymphocytic choriomeningitis virus, Retroviridae: retroviruses, all HTL viruses, human T-cell leukaemia virus, oncornaviruses, spumaviruses, lentiviruses, all HI viruses, Filoviridae: Marburg and Ebola virus, slow-virus infections, prions, oncoviruses and leukaemia viruses.

The organophosphorus compounds used according to the invention are consequently suitable for combating the following viral infections:
eradication of papillomaviruses to prevent tumours, in particular tumours of the reproductive organs caused by papillomaviruses in humans, eradication of JC viruses and BK viruses, eradication of herpesviruses, eradication of human herpesvirus 8 to treat Kaposi's sarcoma, eradication of cytomegaloviruses before transplantations, eradication of Epstein-Barr viruses before transplantation and to prevent tumours associated with Epstein-Barr viruses, eradication of hepatitis viruses to treat chronic liver disease and to prevent liver tumours and cirrhosis of the liver, eradication of coxsackie-viruses in cardiomyopathy, eradication of coxsackie-viruses in diabetes mellitus patients, eradication of immunodeficiency viruses in humans and animals, treatment of accompanying infections in AIDS patients, treatment of respiratory tract inflammation of viral causation (laryngeal papilloma, hyperplasia, rhinitis, pharyngitis, bronchitis, pneumonia), of the sensory organs (keratoconjunctivitis), of the nervous system (poliomyelitis, meningoencephalitis, encephalitis, subacute sclerosing

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panencephalitis, SSPE, progressive multifocal leukoencephalopathy, lymphocytic choriomeningitis), of the gastrointestinal tract (stomatitis, gingivostomatitis, oesophagitis, gastritis, gastroenteritis, diarrhoea), of the liver and gall system (hepatitis, cholangitis, hepatocellular carcinoma), of the lymphatic tissue (mononucleosis, lymphadenitis), of the haemopoietic system, of the reproductive organs (mumps orchitis), of the skin (warts, dermatitis, herpes labialis, herpes febrilis, herpes zoster, shingles), of the mucous membranes (papillomas, conjunctival papillomas, hyperplasia, dysplasia), of the cardiovascular system (arteriitis, myocarditis, endocarditis, pericarditis), of the kidney/urinary system, of the reproductive organs (anogenital lesions, warts, genital warts, sharp condylomas, dysplasia, papillomas, cervical dysplasia, condyloma acuminatum, epidermodysplasia verruciformis), of the locomotory organs (myositis, myalgia), treatment of foot-and-mouth disease in cloven-hoofed animals, of Colorado tick fever, Dengue syndrome, of haemorrhagic fever, of early summer meningoencephalitis (FSME) and of yellow fever.

The described compounds, i.e. the organophosphorus compounds of the formulae (I), (III) and (IV) and esters and amides thereof on the phosphino group and salts thereof exhibit strong cytotoxic activity against uni- and multicellular parasites, in particular against the causative organisms of malaria and sleeping sickness. The compounds according to the invention are accordingly usable for the treatment of infective diseases which are caused in humans and animals by viruses, bacteria, parasites and fungi. The compounds are also suitable for the prevention of diseases which are caused by viruses, bacteria, parasites and fungi, in particular for the prophylactic treatment of malaria and of sleeping sickness.

The organophosphorus compounds used according to the invention, which generally include for this purpose pharmaceutically acceptable salts, amides, esters, a salt of such an ester or also compounds which, on administration, provide the compounds used according to the invention as metabolites or breakdown products (also known as "prodrugs"), may be formulated for administration in any suitable manner analogous to known agents having an antiinfective action (mixed with a non-toxic, pharmaceutically acceptable excipient).

Pharmaceutically acceptable salts of the compounds include salts which the compounds of the formulae (I), (III) and (IV) according to the invention form in their protonated form as an ammonium salt of inorganic or organic acids, such as hydrochloric acid, sulfuric acid, citric acid, maleic acid, fumaric acid, tartaric acid, p-toluenesulfonic acid.

Particularly pharmaceutically suitable salts are also those formed by suitable selection of X_3 and X_4, such as sodium salt, potassium salt, calcium salt, ammonium salt, ethanolamine salt,

triethylamine salt, dicyclohexylamine salt and salts of an amino acid such as arginine salt, aspartic acid salt, glutamic acid salt.

The activity of the substances is determined using a test system. This system is based upon in vitro measurement of the inhibition of growth of bacteria, parasites, viruses, fungi or plants. Test methods known to the person skilled in the art are in part used for this purpose.

For example, antimalarial activity is determined by measuring the inhibition of the growth of malaria parasites in blood cultures.

Antibacterial activity is determined on the basis of measuring the inhibition of bacterial growth on nutrient media and in liquid cultures.

Antiviral activity is determined on the basis of the formation of viral elements in cell cultures.

Fungicidal activity is determined on the basis of inhibition of fungal growth on nutrient media and in liquid cultures.

Some of the microorganisms which are to be investigated may only be investigated in animal models. In this case, the appropriate models will then be used.

Substances which exhibit activity in in vitro measurement systems are then further investigated in in vivo models. Antiparasitic, antiviral, fungicidal or antibacterial activity is further evaluated in the appropriate animal models.

Screening for herbicidal activity is determined by means of algal systems and measurement of isoprene emissions from plants under standard conditions.

The pharmaceutically active agents may be prepared in dosage units in the form of pharmaceutical preparations. This means that the preparation is in the form of individual components, for example tablets, coated tablets, capsules, pills, suppositories and ampoules, the active substance content of which corresponds to a fraction or multiple of an individual dose. The dosage units may contain, for example 1, 2, 3 or 4 individual doses or 1/2, 1/3 or 1/4 of an individual dose. An individual dose preferably contains the quantity of active substance which is administered at one time and usually corresponds to a whole, half, third or quarter of a daily dose.

Non-toxic, inert, pharmaceutically suitable excipients should be taken to mean solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all kinds.

Preferred pharmaceutical preparations which may be mentioned are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays. Tablets, coated tablets, capsules, pills and granules may contain the active substances together with conventional excipients, such as (a) fillers and extenders, for example starches, lactose, cane sugar, glucose, mannitol and silica, (b) binders, for example carboxymethylcellulose, alginates, gelatine, polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) suspending agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) dissolution retardants, for example paraffin and (f) resorption accelerators, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol, glycerol monostearate, (h) adsorbents, for example kaolin and bentonite and (i) lubricants, for example talcum, calcium and magnesium stearate and solid polyethylene glycols or mixtures of the substances stated in (a) to (i).

The tablets, coated tablets, capsules, pills and granules may be provided with conventional coatings and shells optionally containing opacifying agents and may also be composed such that they release the active substances only with a delay or preferably in a particular part of the intestinal tract, wherein polymeric substances and waxes may, for example, be used as the matrices.

The active substance or substances, optionally together with one or more of the above-stated excipients, may also be present in microencapsulated form.

In addition to the active substance or substances, suppositories may contain conventional water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cocoa butter and higher esters (for example C_{14} alcohol with C_{16} fatty acid) or mixtures of these substances.

In addition to the active substance or substances, ointments, pastes, creams and gels may contain conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, gum tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silica, talcum and zinc oxide or mixtures of these substances.

In addition to the active substance or substances, powders and sprays may contain conventional excipients, for example lactose, talcum, silica, aluminium hydroxide, calcium

silicate and polyamide powder or mixtures of these substances. Sprays may additionally contain conventional propellants, for example chlorofluorocarbons.

In addition to the active substance or substances, solutions and emulsions may contain conventional excipients, such as solvents, solubilising agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, peanut oil, corn oil, olive oil, castor oil and sesame oil, glycerol, glycerol formal, tetrahydrofurfuryl alcohol, polyethylene glycols and sorbitan fatty acid esters or mixtures of these substances.

For parenteral administration, the solutions and emulsions may also be present in sterile, isotonic form.

In addition to the active substance or substances, suspensions may contain conventional excipients, such as liquid diluents, for example water, ethyl alcohol, propylene glycol, suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and gum tragacanth or mixtures of these substances.

The stated formulations may also contain colorants, preservatives and odour- or flavour-enhancing additives, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The active substances of the formulae (I), (III) and (IV) should preferably be present in the pharmaceutical preparations listed above in a concentration of approx. 0.1 to 99.5 wt.%, preferably from approx. 0.5 to 95 wt.%, of the complete mixture.

Apart from the compounds of the formulae (I), (III) and (IV), the pharmaceutical preparations may also contain further pharmaceutical active substances.

The compounds may be used together with hitherto described substances having antibacterial, antiviral, antimycotic and antiparasitic properties. Such substances in particular include compounds which have already been used in therapeutic applications or are still used. Substances which are suitable for this purpose are in particular those listed in the Red List or in Simon/Stille, Antibiokia-Therapie in Klinik und Praxis, 9th edition, 1998, Schatauer Verlag, or on the Internet at http://www.customs.treas.gov/imp-exp/rulings/harmoniz/hrm129.html. The derivatives may in particular be present with

penicillins, benzylpenicillin (penicillin G), phenoxypenicillins, isoxazolylpenicillins, aminopenicillins, ampicillin, amoxicillin, bacampicillin, carboxypenicillin, ticarcillin, temocillin, acylaminopenicillins, azlocillin, mezlocillin, piperacillin, apalcillin, mecillinam, cephalosporins, cefazolin group, cefuroxime group, cefoxitin group, cefoxitin, cefotetan, cefmetazole, latamoxef, flomoxef, cefotaxime group, cefozidime, ceftazidime group, ceftazidime, cefpirome, cefepime, conventional cephalosporins, cefsulodin, cefoperazone, oral cephalosporins of the cephalexin group, loracarbef, cefprozil, new broad-spectrum oral cephalosporins, cefixime, cefpodoxime-proxetil, cefuroxime-axetil, cefetamet, cefotiam-hexetil, cefdinir, ceftibuten, other ß-lactam antibiotics, carbapenem, imipenem/cilastatin, meropenem, biapenem, aztreonam, ß-lactamase inhibitors, clavulanic acid/amoxicillin, clavulanic acid/ticarcillin, sulbactam/ampicillin, tazobactam/piperacillin, tetracyclines, oxytetracycline, rolitetracycline, doxycycline, minocycline, chloramphenicol, aminoglycosides, gentamicin, tobramycin, netilmicin, amikacin, spectinomycin, macrolides, erythromycin, clarithromycin, roxithromycin, azithromycin, dirithromycin, spiramycin, josamycin, lincosamides, clindamycin, fusidic acid, glycopeptide antibiotics, vancomycin, teicoplanin, pristinamycin derivatives, fosfomycin, antimicrobial folic acid antagonists, sulfonamides, co-trimoxazole, trimethoprim, other diaminopyrimidine-sulfonamide combinations, nitrofurans, nitrofurantoin, nitrofurazone, gyrase inhibitors (quinolones), norfloxacin, ciprofloxacin, ofloxacin, sparfloxacin, enoxacin, fleroxacin, pefloxacin, lomefloxacin, Bay Y3118, nitroimidazoles, antimycobacterial agents, isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, streptomycin, capreomycin, prothionamide, terizidone, dapsone, clofazimine, topical antibiotics, bacitracin, tyrothricin, polymyxins, neomycin, kanamycin, paromomycin, mupirocin, antiviral agents, acyclovir, ganciclovir, azidothymidine, didanosine, zalcitabine, thiacytidine, stavudine, ribavirin, idoxuridine, trifluridine, foscarnet, amantadine, interferons, tibol derivatives, proteinase inhibitors, antimycotics, polyenes, amphotericin B, nystatin, natamycin, azoles, azoles for septic therapy, miconazole, ketoconazole, itraconazole, fluconazole, UK-109,496, azoles for topical use, clotrimazole, econazole, isoconazole, oxiconazole, bifonazole, flucytosine, griseofulvin, ciclopirox olamine, tolnafnate, naftifine, terbinafine, amorolfine, anthraquinones, betulinic acid, semianthraquinones, xanthones, naphthoquinones, arylamino alcohols, quinine, quinidines, mefloquine, halofantrine, chloroquine, amodiaquine, acridine, benzonaphthyridine, mepacrine, pyronaridine, dapsone, sulfonamides, sulfadoxine, sulfalenes, trimethoprim, proguanil, chlorproguanil, diaminopyrimidines, pyrimethamine, primaquine, aminoquinolines, WR 238,605, tetracycline, doxycycline, clindamycin, norfloxacin, ciprofloxacin, ofloxacin, artemisinin, dihydroartemisinin, 10b artemether, arteether, atresunate, atovaquone, suramin, melarsoprol, nifurtimox, stibogluconate sodium, pentamidine, amphotericin B, metronidazole, clioquinol, mebendazole, niclosamide,

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praziquantel, pyrantel, tiabendazole, diethylcarbamazine, ivermectin, bithionol, oxamniquine, metrifonate, piperazine, embonate.

The organophosphorus compounds may furthermore be present in the pharmaceutical preparations in combination with sulfonamide, sulfadoxine, artemisinin, atovaquone, quinine, chloroquine, hydroxychloroquine, mefloquine, halofantrine, pyrimethamine, armesin, tetracyclines, doxycycline, proguanil, metronidazole, praziquantel, niclosamide, mebendazole, pyrantel, tiabendazole, diethylcarbazine, piperazine, pyrivinium, metrifonate, oxamniquine, bithionol or suramin or two or more of these substances.

The above-stated pharmaceutical preparations are produced in the conventional manner using known methods, for example by mixing the active substance or substances with the excipient or excipients.

The stated preparations may be administered to humans and animals orally, rectally, parenterally (intravenously, intramuscularly, subcutaneously), intracisternally, intravaginally, intraperitoneally, topically (powders, ointments, drops) and for the treatment of infections in cavities, body cavities. Suitable preparations which may be considered are solutions for injections, solutions and suspensions for oral therapy, gels, infusion formulations, emulsions, ointments or drops. Topical treatment may be performed using ophthalmological and dermatological formulations, silver and other salts, ear drops, eye ointments, powders or solutions. Administration to animals may also be achieved via the feed or drinking water in suitable formulations. Gels, pulverulent formulations, powders, tablets, controlled-release tablets, premixes, concentrates, granules, pellets, tablets, boli, capsules, aerosols, sprays, inhalation formulations may also be used in humans and animals. The compounds according to the invention may also be incorporated into other supports, such as for example plastics (plastic chains for topical treatment), collagen or bone cement.

It has in general proved advantageous in both human and veterinary medicine to administer the active substances of the formula (I), (III) and (IV) in total quantities of approx. 0.05 to approx. 600, preferably of 0.5 to 200 mg/kg body weight per 24 hours, optionally in the form of two or more individual doses in order to achieve the desired results. An individual dose preferably contains the active substance or substances in quantities of approx. 1 to approx. 200, in particular of 1 to 60 mg/kg body weight. It may, however, be necessary to deviate from the stated dosages, in particular as a function of the nature and body weight of the patient to be treated, the nature and severity of the disease, the nature of the preparations and the route of administration of the pharmaceutical preparation and the period of time over which administration is performed.

In some cases, it may accordingly be sufficient to use less than the above-stated quantity of active substance, while in other cases more than the above-stated quantity of active substance must be used. The person skilled in the art will use his/her skill to determine the optimum dosage and route of administration required in each particular case.

The compounds according to the invention may be given to animals in conventional concentrations and preparations together with feed or feed preparations or with drinking water.

The compounds according to the invention are furthermore ideally usable as bactericides, fungicides and herbicides in plants.

If the structure of the compound is known, it is generally possible for the person skilled in the art to develop a production process by analogy with known processes. The production of some compounds according to the invention is stated below by way of example:

Example 1: 5-[2-(Phosphono)ethyl]-N-hydroxypyrrolidin-2-one (1)

N-Fluorenylmethoxycarbonyl-pyrrolidin-2-yl-methanol (**1a**

A solution of 476 g (1.85 mol) of chloroformic acid 1-(9-fluorenylmethyl) ester (F-MOC) in 1 l of dioxane is slowly added dropwise with ice cooling to a solution of 182 g (1.8 mol) of pyrrolidin-2-yl-methanol in 1200 ml of dioxane and 1800 ml of a 10% sodium carbonate solution. The mixture is stirred for 4 h at this temperature and for 8 h at room temperature, poured into 1.5 l of ice water and extracted with diethyl ether. The ice-cooled aqueous phase is weakly acidified with dilute HCl, left to stand overnight at 0°C and the product **1a** is then filtered with good purity and yield.

O-(Methanesulfonylmethyl)-N-fluorenylmethoxycarbonyl-pyrrolidine (**1b**)

470 g (1.4 mol) of **1a** are redissolved in 300 ml of absolute pyridine and combined while cold with 400 g (3.5 mol) of methanesulfonyl chloride. The mixture is stirred under argon initially for 16 h at 0°C and then for a further 3 h at RT. Once the mixture has been poured onto ice, extraction is performed repeatedly with diethyl ether and the organic phase is washed in succession with ice-cold dilute HCl, $NaHCO_3$ and water. After drying over $MgSO_4$ and evaporation, **1b** is obtained, which may be purified by recrystallisation from acetone/petroleum ether.

2-(Iodomethyl)-N-fluorenylmethoxycarbonyl-pyrrolidine (**1c**)

3 equivalents (359.7 g) of NaI in acetone are added to a solution of 331 g (0.8 mol) of **1b** in acetone. After 12 hours' stirring at RT, the mixture is filtered, the filtrate added to 800 ml of water, which had been combined with sodium thiosulfate. After repeated extraction with diethyl ether, the extracts were combined, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. Leaving the mixture to stand at low temperature initially yields an oil, which may be recrystallised from petroleum ether.

2-[2-(Dimethylphosphono)ethyl]-pyrrolidine (**1d**)

190 ml of a 1.6 M solution of n-butyllithium in hexane (corresponding to 0.30 mol) were added dropwise at –78°C under argon to 37.2 g (0.3 mol) of methanephosphonic acid dimethyl ester in 900 ml of dry THF. Stirring is continued for a further 15 minutes at this temperature to permit complete formation of the carbanion.

133.9 g (0.3 mol) of **1c** in 300 ml of dry THF were added dropwise to this solution at –78°C with stirring. Once the temperature has risen to room temperature, stirring is continued for a further 4 h. 85.15 g (1 mol) of piperidine is then added and the mixture stirred overnight. The mixture is filtered, the filtrate is poured into 2 l of water, the organic phase separated and the aqueous phase extracted 4 times with 100 ml portions of dichloromethane. Once the combined organic phases have been dried over $MgSO_4$, the solvent is removed and the residue fractionally distilled under a vacuum. 2-[2-(Dimethylphosphono)ethyl]-pyrrolidine (**1d**) is obtained as a colourless oil at yields of 30-40%.

5-[2-(Dimethylphosphono)ethyl]pyrrolidinone (**1e**)

A solution of 60 mmol of dimethyldioxirane in 120 ml of dry acetone is added dropwise to a solution, cooled to 0°C, of 3.32 g (15 mmol) of **1d** in 50 ml of dry acetone. The mixture is stirred for 30 min at 0°C and the solvent is then stripped out under a vacuum. The resultant crude product is recrystallised from isopropanol. 5-[2-(Dimethylphosphono)ethyl]pyrrolidinone (**1e**) is obtained in moderate yield as colourless crystals.

Dimethyldioxirane is produced in accordance with a method in Org. Syntheses IX, 288.

5-[2-(Phosphono)ethyl]-N-hydroxy-pyrrolidin-2-one (**1f**)

3.06 g (20 mmol) of trimethylbromosilane are added dropwise to a solution, cooled to 0°C, of 1.19 g (5 mmol) of **1e** in 50 ml of dry acetonitrile. The mixture is stirred for 3 h at RT, then the solvent is stripped out under a vacuum, the residue is redissolved with 20 ml of ice water, the mixture is stirred for 1 h at room temperature, extracted twice with 20 ml portions of ether, a pH value of 4.5 is established with 2 M NaOH and the water is then stripped out in a Rotavapor rotary evaporator at a maximum of 50°C. The solid residue is crystallised from

methanol/ethyl acetate. 5-[2-(Phosphono)ethyl]-N-hydroxy-pyrrolidin-2-one (**1f**) is obtained in good yield in the form of yellowish microcrystals.

Example 2: 3-(Phosphonomethyl)-N-hydroxy-pyrrolidin-2-one (2)

3-Methyl-N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2a**)
A solution of 120 mmol of sodium ethanolate in 50 ml of absolute ethanol is added dropwise at 0°C with exclusion of moisture to a solution of 20.37 g (120 mmol) of O-(2-trimethylsilyethyl)hydroxylamine hydrochloride in 100 ml of absolute ethanol. Any precipitated NaCl is filtered out with an argon sintered glass filter. The ethanol is removed from the filtrate under reduced pressure and, once argon has been passed through the residue, the latter is redissolved with absolute toluene. 1 mol% of $RhCl_3$*3 H_2O, 5 mol% of DMAP and, dropwise, 5.01 g (50 mmol) of 2-methylbutyrolactone are added thereto at 0°C. The mixture is allowed to thaw and is stirred overnight while being refluxed on the water separator. After cooling, volatile constituents are stripped out under a vacuum at 50°C in a Rotavapor rotary evaporator, a weakly yellow coloured oil being left behind. Redissolution in 50 ml of ether, filtration through a short SiO_2 column and stripping of the solvent gives rise to 3-methyl-N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2a**) in moderate yield as a virtually colourless oil, which is obtained in good purity.

3-Bromomethyl-N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2b**)
50 mmol of **2a**, dissolved in 30 ml of absolute carbon tetrachloride, are combined with 1.2 equivalents of N-bromosuccinimide and refluxed for 12 h. Small quantities of azobisisobutyronitrile (AIBN) are added at hourly intervals. After cooling, the product is filtered from succinimide, the latter is washed with CCl_4 and the combined CCl_4 phases are evaporated under reduced pressure. The resultant oil may be chromatographed on SiO_2, **2b** being obtained in poor yield.

3-(Diethylphosphonomethyl)-N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2c**)
100 mmol (17.3 ml) of triethyl phosphite are combined with 100 mmol of **2b** and heated to 150°C for 0.5 h without solvent. After cooling, the mixture is evaporated under reduced pressure and the yellowish brown oil is chromatographed on SiO_2 with chloroform/methanol in a 25:1 ratio. Once volatile constituents have been stripped out, **2c** is obtained in moderate yield as a yellow oil.

3-(Phosphonomethyl)-N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2d**)
4 equivalents (120 mmol, 15.4 ml) of trimethylbromosilane are added dropwise with ice cooling to 30 mmol of **2c** in 50 ml of absoluted acetonitrile, the mixture is stirred for 15 min

at the same temperature, then for 2 h at RT, evaporated under reduced pressure until a yellowish oil is obtained, the product is redissolved in 100 ml of water and hydrolysed for 1 h at RT (pH less than 1). This solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at 45°C. The resultant yellow-brown oil is redissolved in water and a pH of 4.5 to 5.0 is established. After washing with ice water, **2d** is obtained as a virtually colourless sodium salt at a yield of 50%.

3-(Phosphonomethyl)-N-hydroxy-pyrrolidin-2-one (**2e**)

5.3 mmol of BF_3 etherate are added to a solution of 2.65 mmol of **2d** in absoluted acetonitrile and stirred for 0.5 h at room temperature. Once the solution has been evaporated under reduced pressure, it is redissolved in 40 ml of ethyl acetate, washed with 3% common salt solution, dried over $MgSO_4$, filtered through a membrane filter and the solvent is stripped out under reduced pressure. The crude product may be recrystallised from MeOH/EtOH, the product being obtained in pure form and good yield.

Example 3: 4-(Phosphonomethyl)-N-hydroxy-pyrrolidin-2-one (3)

4-Methyl-2[5H]-furanone (**3a**)

10 g of 3-methylglutaric acid monoethyl ester and 31 g of lead tetraacetate dissolved in 400 ml of absolute CCl_4 are heated to boiling under argon. After 10 minutes' illumination by means of a tungsten daylight lamp, 23.1 g of iodine are added within 45 min while illumination is continued. After cooling, the mixture is filtered, the filtrate washed with aqueous sodium thiosulfate solution, soda solution and water, dried over $MgSO_4$ and evaporated under reduced pressure. The gamma-iodine ester **3a'** is obtained as a oil which may be further reacted without further purification. 18.4 g of freshly precipitated silver acetate and 24 g of acetic anhydride are heated to 120°C in 82 ml of glacial acetic acid for 1 hour, 19.1 g of the gamma-iodine ester **3a'** are added and the mixture refluxed for a further 2 hours. The mixture is then kept for 15 h at RT, combined with 300 ml of ether and filtered. Once the filtrate has been washed with water and aqueous soda solution, the aqueous phase is extracted again with ether, the combined organic extracts are dried over $MgSO_4$ and evaporated under reduced pressure. Once this oil has been redissolved in 70 ml of 2 N NaOH, 10 ml of EtOH and 50 ml of water, the mixture is repeatedly extracted with ether, the ether phases being quantitatively discarded. The aqueous phase, acidified with 150 ml of 6 N HCl, is continuously extracted with ether and, after drying over $MgSO_4$ and evaporation under reduced pressure, is distilled (102-105°C at 34 Torr). 4.4 g of 4-methyl-2[5H]-furanone (**3a**) are obtained.

The remaining steps for preparing **3** follow the synthesis sequence described in **2** by the introduction of O-(2-trimethylsilylethyl)-hydroxylamine hydrochloride, NBS, triethyl phosphite and the hydrolyses of phosphonic acid esters by trimethylbromosilane and the liberation of the cyclic hydroxamic acid by BF_3 etherate. Reference may also be made to T.Sakamoto, Y.Kikugawa *J. Org. Chem.* **1994**, *59*, 929-931 with regard to the synthesis sequence.

Example 4: N-Hydroxy-3-amino-4-(phosphonomethyl)-pyrrolidin-2-one (4)

2-Phenyl-4-(2-acetoxy-1-acetoxymethyl-ethylidene)-2-oxazolin-5-one (**4a**)

0.2 mol of hippuric acid, 0.6 mol of acetic anhydride, 0.24 mol of 1,3-diacetoxyacetone and 0.1 mol of anhydrous lead(II) acetate are initially introduced into 500 ml of THF and refluxed for 16 h under argon. After cooling to RT, inorganic salts are filtered out, the mixture is evaporated under reduced pressure, redissolved in 500 ml of toluene, gaseous hydrogen sulfide is introduced until PbS ceases to precipitate and, after filtration, the mixture is reevaporated. The product is chromatographed on SiO_2 with hexane/chloroform as the solvent mixture, **4b** being obtained at a yield of 73%.

Diacetoxyacetone is synthesised in accordance with a method of A.O.L. Fischer, H. Mildbrand *Ber.Dt.chem.Ges. 57*, 707, **1924**.

2-Amino-3-methoxy-butyric acid (**4b**)

A solution of 31.8 mol of **4a** in 150 ml of dioxane is combined with 1 g of Pd/C and hydrogenated at standard pressure until 10 mol of hydrogen have been absorbed (4-6 h). Once the catalyst has been filtered out, the mixture is evaporated to dryness, redissolved in 40 ml of water and 60 ml of conc. HCl, refluxed for 4 h and kept overnight in the refrigerator. The filtered solution is evaporated, redissolved in 50 ml of water and purified on Amberlite IR 120, H^+ ion exchanger by elution with 300 ml of aqueous ammonia solution. The mixture is boiled until no ammonia is any longer detectable, reevaporated under reduced pressure and recrystallised.

Alpha-amino-beta-methoxy-gamma-butyrolactone (**4c**)

25 mmol of **4b** are stirred for 15 min at RT with 20 ml of 2.5% HCl. The solution is evaporated to dryness and extracted overnight with chloroform in a Soxhlet apparatus. Once the solvent has been stripped out under reduced pressure, the lactone **4c** is obtained in virtually quantitative yield.

N,N-Dibenzylamino-beta-methoxy-gamma-butyrolactone (**4d**)

0.2 mol of **4c**, 72 g of K_2CO_3 and 300 mg of tetrabutylammonium iodide and 500 mg of 18-crown-6 are suspended in 100 ml of ethanol and heated to 40°C. 0.65 mol of benzyl bromide are added dropwise within 15 min, the mixture is stirred for 12 h at RT, the phases are separated, the aqueous phase washed twice with 75 ml portions of ether, the organic phases are combined, washed with saturated NaCl solution and dried over $MgSO_4$. After evaporation under reduced pressure, the mixture is chromatographed on a short silica gel column.

N,N-Dibenzylamino-beta-(bromomethyl)-butyrolactone (**4e**)

2.23 g (6.18 mmol) of CBr_4 are added to a mixture of 4.12 mmol of **4d**, 6.18 mmol of PPh_3 and 20 ml of absolute acetonitrile. The mixture is stirred for 20 h at RT, the solvent removed under reduced pressure and chromatographed on silica gel with ethyl acetate/n-hexane as solvent. **4e** is obtained in variable yield as a yellowish oil.

N,N-Dibenzylamino-beta-(dimethylphosphonomethyl)-butyrolactone (**4f**)

40 mmol of **4e** are refluxed for 0.5 to 1 h with 1 equivalent of trimethyl phosphite in toluene. After cooling, the mixture is evaporated under reduced pressure and the remaining oil is chromatographed on SiO_2 with chloroform/methanol as the mobile solvent. Once volatile constituents have been stripped out, **4f** is obtained in moderate yield.

N,N-Dibenzylamino-beta-(dimethylphosphonomethyl)-butyrolactam (**4g**)

A solution of 100 ml of sodium ethanolate in 50 ml of absolute ethanol is added dropwise at 0°C with exclusion of moisture to a solution of 120 mmol of O-benzylhydroxylamine hydrochloride in 100 ml of absolute ethanol. Any precipitated NaCl is filtered out with an argon sintered glass filter. The ethanol is removed from the filtrate under reduced pressure and, once argon has been passed through the residue, the latter is redissolved with absolute toluene. 1 mol% of $RhCl_3$ 3 H_2O, 5 mol% DMAP and, dropwise, 50 mmol of **4f** are added thereto at 0°C. The mixture is allowed to thaw and is stirred overnight while being refluxed on the water separator. After cooling, volatile constituents are stripped out under a vacuum at 50°C in a Rotavapor rotary evaporator, an oil being left behind. Redissolution in 40 ml of ethyl acetate, filtration through a short SiO_2 column and stripping of the solvent gives rise to (**4g**) in moderate yield as a yellow oil, which is obtained in good purity.

N-Hydroxy-3-amino-4-(dimethylphosphonomethyl)-pyrrolidin-2-one (**4h**)

30 mmol of **4g** in 60 ml of methanol and 10 ml of formic acid are hydrogenated with 5 mol% Pd/C (10-20%) under standard pressure at RT for 13 h. Once the catalyst has been filtered out, the mixture is evaporated under reduced pressure and reacted without further purification.

N-Hydroxy-3-amino-4-(Phosphonomethyl)-pyrrolidin-2-one (**4i**)

35 mmol of trimethylbromosilane are added dropwise with ice cooling to 10 mmol of **4h** in 20 ml of absoluted acetonitrile, the mixture is stirred for 15 min at the same temperature, then for 2 h at RT, evaporated under reduced pressure until a yellowish oil is obtained, the product is redissolved in 100 ml of water and hydrolysed for 1 h at RT. This solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at 45°C. The resultant dark oil is redissolved in water and a pH of 6.0 is established. Precipitating **4i** is filtered out and washed with ice water. **4i** is obtained as the sodium salt in the form of beige crystals at a yield of 35-40%.

Example 5: N,2-Dihydroxy-5-(2-phosphonoethyl)-pyrrole (5)

N-Benzyloxy-5-[2-(dimethylphosphono)ethyl]pyrrolidin-2-one (**5a**)

20 mmol of 5-[2-(dimethylphosphono)ethyl]pyrrolidinone (**1e**) are stirred overnight at room temperature with 1.2 equivalents of benzyl bromide, 10 mg of tetrabutylammonium iodide and 1.3 equivalents of triethylamine in 30 ml of THF, are then poured into ice water, repeatedly extracted with small quantities of ether, the diethyl ether phase is washed with cold dilute HCl and with saturated common salt solution, dried over $MgSO_4$, evaporated and the crude product chromatographed on silica gel with chloroform/methanol 25:1. **5a** is obtained in good yield.

N-Benzyloxy-3-phenylseleno-5-[2-(dimethylphosphono)ethyl]pyrrolidin-2-one (**5b**)

2.0 mmol of **5a**, which is dissolved in 1 ml of absolute THF and stirred for 20 min at –78°C, is added at the same temperature to 2.4 mmol of diisopropylamide in 3 ml of THF (LDA, produced from 0.35 ml of diisopropylamine and 1.6 ml of 1.65 M n-BuLi in hexane under argon at –78°C). 2.4 mmol of diphenyl diselenide, dissolved in 1 ml of THF and 1.2 mmol of HMPT, are added at –78°C to the enolate of **5a**. The reaction mixture is stirred for 40 min at –78°C and for 1.5 h at –40°C. Quenching with 0.1 N HCl and subsequent repeated extraction with ether yields, after chromatography on silica gel, a yellowish oil **5b** of a characteristic odour.

N-Benzyloxy-2-hydroxy-4-[2-(dimethylphosphono)ethyl]pyrrole (**5c**)

0.2 mmol of the phenylseleno compound **5b**, dissolved in 1 ml of absolute THF, is combined with 30 µl of glacial acetic acid, 140 µl of Perhydrol (30% hydrogen peroxide solution) are added dropwise with ice cooling and the mixture stirred for 30 min at the same temperature. The solution is poured into cold, saturated aqueous sodium hydrogen carbonate solution, the mixture extracted with ether, dried over $MgSO_4$, evaporated under reduced pressure and the crude product chromatographed on silica gel. **5c** is obtained in good yield as a yellowish oil.

N,2-Dihydroxy-4-[2-(dimethylphosphono)ethyl]pyrrole (**5d**)

0.15 mmol of **5c** is placed in 50 ml of absolute EtOH, a spatula-tipfull of 10% Pd on activated carbon is added and the mixture hydrogenated for 1 h at RT in a standard pressure hydrogenation apparatus with vigorous stirring. Once the catalyst has been filtered out, the mixture is evaporated and the crude product is reacted without further purification.

N,2-Dihydroxy-5-(2-phosphonoethyl)-pyrrole (**5e**)

4 equivalents (60 mmol, 8 ml) of trimethylbromosilane are added dropwise with ice cooling to 15 mmol of **5d** in 50 ml of absoluted acetonitrile, the mixture is stirred for 15 min at the same temperature, then for 2 h at RT, evaporated under reduced pressure until a yellowish oil is obtained, the product is redissolved in 80 ml of water and hydrolysed for 1 h at RT (pH < 1). This solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at a maximum of 45°C. The resultant oil is redissolved in water and a pH of 4.5 to 5.0 is established with $NaHCO_3$. **5e** is removed by suction filtration and, after washing with iced water, **5e** is obtained as a virtually colourless sodium salt at a yield of 40%.

Example 6: N-Hydroxy-3-[2-(phosphono)ethyl]-1H-pyridone (6)

2-Bromo-3-(bromomethyl)pyridine (**6a**)

10 g (58.1 mmol) of 2-bromo-3-methylpyridine and 11.4 g (64 mmol) of [sic] are refluxed for 24 h in 250 ml of CCl_4. The succinimide is separated by filtration and the organic phase is washed twice with water. After evaporation under reduced pressure, **6a** is obtained as a colourless liquid by fractional distillation (bp: 90°C, 1 Torr).

2-Bromo-3-[2-(dimethylphosphono)ethyl]pyridine (**6b**)

0.21 mol of MeLi in ether is added dropwise to 100 ml of absolute THF, 0.1 mol of trimethyl phosphite, dissolved in 50 ml of THF, is added dropwise within 15 min in such a manner that the internal temperature slowly reaches 0°C. 0.107 mol of **6a** in 20 ml of THF is then added dropwise at a temperature of –78°C, stirring is continued for a further 30 min at the same temperature, the mixture is allowed to thaw and quenched at 0°C by dropwise addition of 80 ml of 3 M HCl. The organic phase is separated, the aqueous phase extracted three times with 40 ml portions of dichloromethane and, after drying over $MgSO_4$, the combined organic phases are evaporated. The yellow crude product may be purified in a short column on SiO_2.

2-Bromo-3-[2-(dimethylphosphono)ethyl]pyridine N-oxide (**6c**)

100 mmol of **6b** in 60 ml of glacial acetic acid are combined with 2 equivalents of a 40% peracetic acid solution, wherein the temperature should not exceed 50°C. After 5 hours' heating to 50°C and 12 hours' heating to 70°C, the solution is evaporated to half its volume under reduced pressure, poured onto ice and made highly alkaline with 40% aqueous KOH. Triple extraction with chloroform yields, after drying over K_2CO_3 and evaporation under reduced pressure, an N-oxide oil **6c**, which was reacted without further purification.

N-Hydroxy-3-[2-(dimethylphosphono)ethyl]-1H-pyridone (**6d**)

6c is heated in a glass autoclave for 3 h to 120°C in absolute MeOH together with mortar-ground potassium hydroxide, potassium carbonate and tris(3,6-dioxaheptyl)amine. After cooling, the reaction mixture is poured into water, a pH value of 6 is established, the mixture evaporated under a vacuum and, after addition of ethanol, a crude product is obtained which may be recrystallised in moderate yield from ethanol/toluene.

N-Hydroxy-3-[2-(phosphono)ethyl]-1H-pyridone (**6e**)

40 mmol of trimethylbromosilane are added dropwise with ice cooling to 10 mmol of **6d** in 30 ml of absolute acetonitrile, the mixture is stirred for 15 min at the same temperature, then for 2 h at RT, evaporated under reduced pressure until an oil is obtained, the product is redissolved in 20 ml of water and hydrolysed for 1 h at RT (acidic pH). This solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at 45°C. The resultant brown oil is redissolved in water, stirred twice with activated carbon, filtered therefrom and a pH of 5 is established. As a result, **6e** precipitates out, is filtered, washed with ice water and may be recrystallised from MeOH/EtOH.

Example 7: N-Hydroxy-6-[2-(phosphono)ethyl]-1H-pyridone (7)

2-Bromo-6-bromomethylpyridine (**7a**)

10.1 g (58.7 mmol) of 2-bromo-6-methylpyridine, 11.1 g (62.4 mmol) of N-bromosuccinimide (NBS) and 0.1 g (0.6 mmol) of AIBN are heated under argon for 6 h to 110°C in 150 ml of toluene, the mixture simultaneously being illuminated with a tungsten daylight lamp (150 W, >320 nm). After cooling, succinimide is filtered out and the solution evaporated under reduced pressure. Chromatography on silica gel (mobile solvent: hexane/dichloromethane) at first yields 2-bromo-6-dibromomethylpyridine, while **7a** may subsequently be eluted at a yield of up to 45% (mp: 138°C).

2-Bromo-6-[2-(dimethylphosphono)ethyl]pyridine (**7b**)

0.21 mol of MeLi in ether is added dropwise to 100 ml of absolute THF, 0.1 mol of trimethyl phosphite, dissolved in 50 ml of THF, is added dropwise within 15 min in such a manner that the internal temperature slowly reaches 0°C. 0.107 mol of **7a** in 15 ml of THF is then added dropwise at a temperature of –78°C, stirring is continued for a further 30 min at the same temperature, the mixture is allowed to thaw and quenched at 0°C by dropwise addition of 80 ml of 3 M HCl. The organic phase is separated, the aqueous phase extracted repeatedly with 40 ml portions of dichloromethane and, after drying over $MgSO_4$, the combined organic phases are evaporated. The yellow crude product may be chromatographically purified on SiO_2, **7b** being obtained at a yield of 47%.

2-Bromo-6-[2-(dimethylphosphono)ethyl]pyridine N-oxide (**7c**)

50 mmol of **7b** in 50 ml of glacial acetic acid are combined with 2 equivalents of a 40% peracetic acid solution, the temperature varying between 25 and 45°C. After 5 hours' heating to 50°C and 12 hours' heating to 70°C, the solution is poured onto ice and made highly alkaline with 40% aqueous KOH. Triple extraction with chloroform yields, after drying over K_2CO_3 and evaporation under reduced pressure, an N-oxide oil **7c**, which may be recrystallised from ether/ethanol.

N-Hydroxy-6-[2-(dimethylphosphono)ethyl]-1H-pyridone (**7d**)

7c is heated in a glass autoclave for 2.5 h to 100°C in absolute MeOH together with mortar-ground potassium hydroxide, potassium carbonate and tris(3,6-dioxaheptyl)amine. After cooling, the reaction mixture is poured into water, a pH value of 6 is established, the mixture evaporated under a vacuum and, after addition of ethanol, a crude product is obtained which, similarly to **6d**, may be recrystallised in moderate yield.

N-Hydroxy-6-[2-(phosphono)ethyl]-1H-pyridone (**7e**)

40 mmol of trimethylbromosilane are added dropwise with ice cooling to 10 mmol of **7d** in 25 ml of absolute acetonitrile, the mixture is stirred for 10 min at the same temperature, then for 2 h at RT, evaporated under reduced pressure at 45°C until an oil is obtained, the product is redissolved in 20 ml of water and hydrolysed for 1 h at RT. This solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at 45°C. The resultant dark-coloured oil is redissolved in water and a pH of 4.8 is established. As a result, **7e** precipitates out as the sodium salt. After filtration and washing with ice water, **7e** is obtained as a crude product, which may be recrystallised from MeOH/toluene.

Example 8: N-Hydroxy-5-[2-phosphono-2-hydroxy)ethyl]pyrrolidin-2-one (8)

N-Benzyl-2-(1,3-dithioylmethyl)-pyrrolidine (**8a**)

100 mmol (12.0 g) of 1,3-dithiane are weighed out under protective gas, 250 ml of absolute THF are added thereto and a 5% excess of n-BuLi in hexane is added dropwise thereto within 3-5 min at –40°C. The mixture is stirred for 2 h at –25 to –15°C, the temperature is reduced to –60 to –78°C and 100 mmol of 2-iodomethyl-N-benzyloxy-pyrrolidine are slowly added thereto under protective gas. After 5-6 hours' stirring at –20 to –10°C, the temperature is allowed to rise to 0°C and the reaction mixture is placed in the refrigerator for three days. After evaporation to approx. 20 ml, the mixture is poured into three times its volume of water, extraction performed three to five times with chloroform, the organic phases are combined, washed in succession with water, 6% KOH and again with water and the chloroform phase is dried over K_2CO_3. The residue obtained after evaporation under reduced pressure is reacted without further purification.

N-Benzyl-2-(formylmethyl)-pyrrolidine (**8b**)

1.1 g of $CaCO_3$ and 2.5 ml of $Hg(ClO_4)_2$ of a 4 M aqueous solution are added to a solution of 9 mmol of **8a** in 30 ml of THF and 6 ml of water, stirring is continued for a further 5 to 10 min, 150 ml of ether are added thereto and inorganic salts are filtered out. Once the solution has been evaporated under reduced pressure, a coloured crude product remains, which is purified by flash chromatography.

N-Benzyl-2-[2-(diethylphosphono)-2-hydroxy]pyrrolidine (**8c**)

20 g (145 mmol) of diethyl phosphonate and 140 mmol of **8b** are heated under argon to 80 to 85°C for 8 h. After cooling, the mixture is evaporated under reduced pressure and the product **8c** is purified chromatographically on silica gel.

N-Benzyl-2-[2-(diethylphosphono)-2-acetoxy]pyrrolidine (**8d**)

A mixture of 50 mmol of 1-hydroxyphosphonic acid ester **8c**, 75 mmol of triethylamine, 75 mmol of acetic anhydride and 4 mmol of dimethylaminopyridine (DMAP) is left to stand for 14 h at RT and, after addition of 100 ml of ether and 2 N HCl, the etheric phase is washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, evaporated and purified on a short ALOX column.

2-[2-(N-Benzyl-2-[8-(diethylphosphono)-2-acetoxy]pyrrolidine (**8e**)

After addition of 400 mg of PtO_2, a solution of 40 mmol of **8d** in 30 ml of glacial acetic acid is hydrogenated at 70°C for 6 h at standard pressure. Once the catalyst has been filtered out, the mixture is repeatedly extracted with ether in a strongly alkaline medium, the combined

ether extracts are dried over $MgSO_4$, evaporated and the product **8e**, which is obtained in good yield, is directly further reacted.

N-Hydroxy-5-[2-phosphono-2-hydroxy)ethyl]pyrrolidin-2-one (**8f**)
A solution of 70 mmol of dimethyldioxirane in 110 ml of dry acetone is added dropwise to a solution, cooled to 0°C, of 20 mmol of **8e** in 50 ml of dry acetone. The mixture is stirred for 30 min at 0°C and the solvent is then stripped out under a vacuum. A yellow oil is obtained, which may be purified on silica gel with a chloroform/methanol mobile solvent mixture.

N-Hydroxy-5-[(2-diethylphosphono-2-hydroxy)-ethyl]pyrrolidin-2-one (**8g**)
The yellow oil **8f** is stirred overnight with 5 M aqueous KOH in MeOH at RT, then neutralised, MeOH is removed under reduced pressure and the mixture extracted with ether. The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The resultant **8g** is used for the subsequent reactions without further purification.

N-Hydroxy-5-[(2-phosphono-2-hydroxy)-ethyl]pyrrolidin-2-one (**8h**)
80 mmol of trimethylbromosilane are added dropwise to a solution, cooled to 0°C, of 20 mmol of **8g** in 50 ml of dry acetonitrile. The mixture is stirred for 3 h at RT, then the solvent is stripped out under a vacuum, the residue is redissolved with 60 ml of iced water, the mixture is stirred for 1 h at room temperature, extracted three times with 60 ml portions of ether, a pH value of 5.5 to 6.0 is established with 2 M NaOH and the water is then stripped out in a Rotavapor rotary evaporator at a maximum of 45°C. The solid residue is crystallised from methanol/ethyl acetate. N-Hydroxy-5-[(2-phosphono-2-hydroxy)-ethyl]pyrrolidin-2-one (**8h**) is obtained in good yield in the form of yellowish-white microcrystals.

Example 9: 3-(Methylphosphono)-N-hydroxy-succinimide (9)

3-(Bromomethyl-succinic anhydride (**9a**)
In a similar manner to the preparation of N-(2-trimethylsilylethoxy)-pyrrolidin-2-one (**2b**) 50 mmol of 2-methylsuccinic anhydride, dissolved in 30 ml of absoluted carbon tetrachloride, are reacted with 1.2 equivalents of N-bromosuccinimide by refluxing the mixture for 12 h. Small quantities of azobisisobutyronitrile (AIBN) are added at hourly intervals. After cooling, the product is filtered from succinimide, the latter is washed with CCl_4 and the combined CCl_4 phases are evaporated under reduced pressure. The resultant oil may be chromatographed on SiO_2, **9a** being obtained in low yield.

3-[2-(Dimethylphosphono)ethyl]-succinic anhydride (**9b**)

40 mmol of **9a** are refluxed for 0.5 to 1 h with 1 equivalent of trimethyl phosphite in toluene. After cooling, the mixture is evaporated under reduced pressure and the yellowish oil is chromatographed on SiO_2. Once volatile constituents have been stripped out, **9b** is obtained in low yield.

3-[2-(Dimethylphosphono)methyl]-N-benzyloxy-succinimide (**9c**)

1.0 g of benzyloxyamine is heated in a glass autoclave with 1.0 equivalent of **9b** to 180°C for 30 min. After cooling, the oil is evaporated under reduced pressure, a poor crude product yield being observed, and **9c** is further reacted without purification.

3-[2-(Dimethylphosphono)methyl]-N-hydroxy-succinimide (**9d**)

9.28 mmol of the benzyloxy compound **9c** dissolved in 60 ml of ethanol are combined with 700 mg of Pd/C and hydrogenated at standard pressure for 4 h at RT. Once hydrogen absorption has ceased, the catalyst is filtered out, the mixture evaporated under reduced pressure and recrystallised from ethyl acetate/hexane, **9d** being obtained in good yield.

3-[2-Phosphonomethyl]-N-hydroxy-succinimide (**9e**)

110 mmol of trimethylbromosilane are added dropwise to a solution, cooled to 0°C, of 30 mmol of **9g** in 70 ml of dry acetonitrile. The mixture is stirred for 3 h at RT, then the solvent is stripped out under a vacuum, the residue is redissolved with 80 ml of iced water, the mixture is stirred for 1 h at room temperature, extracted three times with 50 ml portions of ether, a pH value of 5.5 to 6.0 is established with $NaHCO_3$ and the water is then stripped out in a Rotavapor rotary evaporator at a maximum of 45°C. The solid residue is crystallised from methanol/acetone. **9e** is obtained in the form of beige crystals in good yield.

Example 10: 1-N-(2-Phosphonoethyl)-3-hydroxy-7-methyl-xanthine (10)

1-N-(2-Dimethylphosphono-ethyl)-7-methylxanthine (**10a**)

50 g of 7-methylxanthine (2,6-dihydroxy-7-methylpurine) are dissolved in 1 l of boiling ethanol and 38 g of 50% potassium hydroxide solution are added thereto. Once the mixture has cooled to 15 to 20°C, the potassium salt of 7-methylxanthine precipitates out, is filtered out and decocted with boiling acetone and boiling absolute ethanol.

A solution of 20 mmol of 2-bromomethylphosphonic acid dimethyl ester and 2 mmol of hexadecyltributyl-phosphonium bromide in 10 ml of toluene is combined with 25 mmol of the potassium salt of 7-methylxanthine and the mixture heated to 100°C for 2 h. Once the reaction mixture has cooled, undissolved fractions are filtered out and the evaporated organic phase is

chromatographed on silica gel with ether/chloroform as mobile solvent. In this manner, both the desired 1-N-(2-dimethylphosphono-ethyl)-7-methylxanthine (**10a**) and, at lower yield, 3-N-(2-dimethylphosphono-ethyl)-7-methylxanthine (**10a'**) are obtained.

1-N-(2-Dimethylphosphono-ethyl)-3-hydroxy-7-methyl-xanthine (**10b**)
A solution of 60 mmol of dimethyldioxirane in 120 ml of dry acetone is added dropwise to a solution, cooled to 0°C, of 25 mmol of **10a** in 50 ml of dry acetone. The mixture is stirred for 30 min at 0°C and the solvent is then stripped out under reduced pressure. The resultant crude product is chromatographed on silica gel, 1-N-(2-dimethylphosphono-ethyl)-3-hydroxy-7-methyl-xanthine (**10b**) being obtained in poor yield.

In a similar manner, 3-N-(2-dimethylphosphonoethyl)-7-methylxanthine (**10a'**) may be converted into 3-N-(2-dimethylphosphono-ethyl)-1-hydroxy-7-methylxanthine (**10b'**).

1-N-(2-Phosphono-ethyl)-3-hydroxy-7-methyl-xanthine (**10c**)
4 equivalents (100 mmol) of trimethylbromosilane are added dropwise with ice cooling to 25 mmol of **10b** in 50 ml of absoluted acetonitrile, the mixture is stirred for 15 min at the same temperature, then for 2 h at RT, evaporated under reduced pressure until an oil is obtained, the product is redissolved in 100 ml of water and hydrolysed for 1 h at RT. In order to remove hexamethyldisiloxane, this solution is extracted twice with $CHCl_3$, back-extracted once with water and the combined aqueous phases are evaporated under reduced pressure at 45°C. The resultant beige oil is redissolved in water and a pH of 6.5 to 7.0 is established. After washing with iced water, **10c** is obtained as a virtually colourless sodium salt at a yield of 55%.

In a similar manner, 3-N-(2-dimethylphosphono-ethyl)-1-hydroxy-7-methyl-xanthine (**10b'**) is reacted with trimethylbromosilane to yield 3-N-(2-phosphono-ethyl)-1-hydroxy-7-methyl-xanthine (**10c'**).

Example 11: N-Hydroxy-1,2,3,4-tetrahydro-1-oxo-3-[2-phosphonoethyl)]-isoquinoline (11)

3-Phenyl-2-aminopropanol (**11a**)
3.0 mol of $LiAlH_4$ are suspended in 900 ml of anhydrous tetrahydrofuran in a heat-treated and argon-flooded three-necked flask fitted with a KPG stirrer and 1.5 mol of phenylalanine are added in portions with ice cooling. The mixture is then refluxed for 6 h, allowed to cool and hydrolysed with crushed ice. The mixture is filtered and the solvent removed under a vacuum. The filtrate is redissolved with CH_2Cl_2, washed with saturated NaCl solution and dried with

Na_2SO_4. Vacuum distillation is then performed. 3-Phenyl-2-aminopropanol **11a** is obtained at a yield of 76%.

1-Phenyl-3-(tetrahydro-2-pyranyloxy)-2-aminopropane (**11b**)

2.5 mol of dihydropyran and 5.3 g of p-toluenesulfonic acid are added to 1.4 mol of 3-phenyl-2-aminopropanol **1** and the mixture then stirred for 20 h at RT. The excess dihydropyran is then removed under a vacuum, the residue redissolved with 700 ml of ethyl acetate and washed with 300 ml portions of saturated $NaHCO_3$ solution and saturated NaCl solution. The mixture is then dried with $MgSO_4$, filtered and the solvent removed under a vacuum. 1-Phenyl-3-(tetrahydro-2-pyranyloxy)-2-aminopropane (**11b**) is obtained at a yield of 63%.

1-Phenyl-3-(tetrahydro-2-pyranyloxy)-2-isocyanopropane (**11c**)

0.88 mol of 1-phenyl-3-(tetrahydro-2-pyranyloxy)-2-aminopropane **11b** are added dropwise to a solution of 3.52 mol of phosgene in 1.5 l of toluene and the mixture then boiled for 3 h at 80°C. The solvent is then removed under a vacuum. The desired product 1-phenyl-3-(tetrahydro-2-pyranyloxy)-2-isocyanopropane **11c** is obtained at a yield of 83%. This is used without further purification.

1,2,3,4-Tetrahydro-1-oxo-3-hydroxymethyl-isoquinoline (**11d**)

A solution of 0.72 mol of 1-phenyl-3-(tetrahydro-2-pyranyloxy)-2-isocyanopropane **11c** in 80 ml of anhydrous acetone is slowly added dropwise to 100 ml of ice-cooled phosphoric acid and stirred for 3 h at RT. Ice water is then added, the mixture stirred for 0.5 h and then extracted with CH_2Cl_2. The organic phase is washed with water, saturated Na_2CO_3 solution, again with water and with saturated NaCl solution and dried with $MgSO_4$. After filtration and removal of the solvent under a vacuum, the product is recrystallised from hexane/benzene, 28% of 1,2,3,4-tetrahydro-1-oxo-3-hydroxymethyl-isoquinoline (**11d**) being obtained.

1,2,3,4-Tetrahydro-1-oxo-3-bromomethyl-isoquinoline (**11e**)

A solution of 180 mmol of PPh_3 in 120 ml of CH_2Cl_2 is added to a solution of 150 mmol of 1,2,3,4-tetrahydro-1-oxo-3-hydroxymethyl-isoquinoline **11c** and 210 mmol of CBr_4 in 150 ml of CH_2Cl_2 and stirred for 20 h at RT. The solvent is then removed under a vacuum and the residue repeatedly recrystallised from benzene. The product 1,2,3,4-tetrahydro-1-oxo-3-bromomethyl-isoquinoline **11e** is obtained at a yield of 31%.

1,2,3,4-Tetrahydro-1-oxo-3-(2-diethylphosphonoethyl)-isoquinoline (**11f**)

66.2 mmol of solution of n-butyllithium (1.15 M) in hexane are added dropwise at –78°C to a solution of 75 mmol of dimethyl methylphosphonate in 120 ml of absolute THF under argon and the mixture stirred for 1.5 h at this temperature. 46.5 mmol of 1,2,3,4-tetrahydro-1-oxo-3-

bromomethyl-isoquinoline **11e** in 50 ml of absolute THF are added dropwise to this solution at –78°C, the mixture stirred for a further 1 h at –78°C and then allowed to rise to RT overnight. 100 ml of water are then added, the aqueous phase separated and extracted 3 times with 50 ml portions of ethyl acetate. The combined organic phases are dried with $MgSO_4$, filtered and the solvent removed under a vacuum. The residue is purified chromatographically (silica gel, hexane/ethyl acetate 5:1). 24% of the desired product 1,2,3,4-tetrahydro-1-oxo-3-(2-diethylphosphonoethyl)-isoquinoline **11f** are obtained.

N-Hydroxy-1,2,3,4-tetrahydro-1-oxo-3-(2-diethylphosphonoethyl)-isoquinoline (**11g**)
5.36 mmol of 1,2,3,4-tetrahydro-1-oxo-3-(2-diehtylphosphonoethyl)-isoquinoline **6** are dissolved in 30 ml of absolute acetone and cooled to 0°C. A solution of 17.15 mmol of dimethyldioxirane is then added dropwise and the mixture stirred for 30 min at 0°C. The solvent is removed under a vacuum and the residue purified chromatographically (silica gel, hexane/ethyl acetate 4:1). 33% of the product N-hydroxy-1,2,3,4-tetrahydro-1-oxo-3-(2-diethylphosphonoethyl)-isoquinoline **11g** are obtained.

N-Hydroxy-1,2,3,4-tetrahydro-1-oxo-3-(2-phosphonoethyl)-isoquinoline (**11h**)
1.77 mmol of N-hydroxy-1,2,3,4-tetrahydro-1-oxo-3-(2-diethylphosphonoethyl)-isoquinoline **11g** are dissolved in 15 ml of absolute CH_2Cl_2 under argon and cooled to 0°C. 10 mmol of trimethylbromosilane are then added dropwise from a syringe, the mixture stirred for a further 1 h at 0°C and then overnight at RT. The solvent is then removed under a vacuum, the residue redissolved in 20 ml of water and stirred for 1 h at RT. 15 ml of $CHCl_3$ are then added and the organic phase separated. The aqueous phase is extracted twice more with 10 ml portions of $CHCl_3$ and the mixture evaporated under a vacuum. The residue is purified chromatographically (silica gel, H_2O/methanol 1:1). The desired product is obtained at a yield of 54%.

Example 12:

The antimalarial activity of the substances stated in Table I was determined using in vitro cultures of the causative organism of malaria, Plasmodium falciparum. The roman numerals refer to the particularly preferred compounds stated on pages [sic] to [sic]. 200 µl of an asynchronous Plasmodium falciparum culture with a 0.4% blood parasite content and a haematocrit of 2% were loaded into each of the wells of a 96 well microtitre plate. A serial dilution series of the compounds was then prepared in steps of three between concentrations of 100 and 1 µmol l^{-1}. The plates are incubated at 37°C, 3% CO_2 and 5% O_2 over a period of 48 hours. 30 µl of medium supplemented with 27 µCi ml^{-1} of [^{3}H]-hypoxanthine were then added to each well. After 24 hours' incubation, the parasites were harvested by filtration

through glass fibre filters and the incorporated radioactivity was measured. Inhibition of parasite growth was measured as the percentage inhibition of tritium incorporation relative to a comparison without the substance. The results for the three different concentrations are stated in Table I.

Table I

Substance	R_5	A	Form used	100 µM inhibition (%)	10 µM inhibition (%)	1 µM inhibition (%)
I	H	C_2H_4	Na salt	98	98	98
III	H	CH_2	Na salt	96	98	63
II	H	CH_2	Na salt	98	87	59
I	H	CH_2CHOH	Na salt	98	97	78
X	H	CH_2	Na salt	89	80	0
X	H	CH_2	Na salt	98	97	98
III	H	CH_2	Na salt pyrrole ring is NH_2-substituted in position 3	98	98	82
VII	H	C_2H_4	Na salt	98	98	98
XXXI	H	C_2H_4	Na salt	97	73	53
XXVIII	H	C_2H_4	Na salt	98	97	82
XXXVIII	H	C_2H_4 N-substituted in position 5	Na salt	92	78	30
XXXVI	H	C_2H_4 in position 3	Na salt	95	80	37

Example 13

The antibacterial action of the substances stated in Table II was determined. The roman numerals refer to the particularly preferred compounds stated on pages 5 to 8.
A dilution series comprising the concentrations 500, 100, 50 and 10 µmol l^{-1} of the individual compounds in LB medium is introduced into 5 culture microtubes in a volume of 0.5 ml. Each of the microtubes was inoculated with 10 µl of an overnight culture of E. coli K12 and shaken

overnight at 37°C. Bacterial growth was assessed on the basis of the turbidity of the medium. The minimum concentration causing inhibition of bacterial growth was determined (minimum inhibition concentration, MIC).

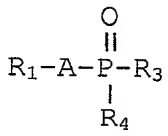
Antibacterial activity with regard to P. aeruginosa was determined in the same manner. The results are shown in Table II.

Table II

Substance	**R_5**	**A**	**Form used**	**E. coli MIC (mg/l)**	**P. aeruginosa 10 mg/l**
I	H	C_2H_4	Na salt	2.5	5
III	H	CH_2	Na salt pyrrole ring is NH_2-substituted in position 3	5	5
II	H	CH_2	Na salt	10	5
I	H	CH_2CHOH	Na salt	2.5	1.25
X	H	CH_2	Na salt	1.25	1.25
X	H	CH_2	Na salt	10	20
III	H	CH_2	Na salt	1.25	10
VII	H	C_2H_4	Na salt	10	40
XXXI	H	C_2H_4	Na salt	10	1.25
XXVIII	H	C_2H_4	Na salt	5	5
XXXVIII	H	C_2H_4 N-substituted in position 5	Na salt	20	80
XXXVI	H	C_2H_4 in position 3	Na salt	40	20

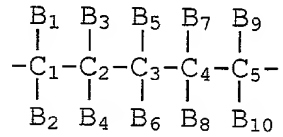
Patent Claims

1. Organophosphorus compounds of the general formula (I)



(I)

wherein A is selected from the group which consists of a (C_{1-9}) alkylene residue, which may comprise one or more double bonds and may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, -C-O-C- and -C-N-C-, wherein the carbon atoms of -C-O-C- and -C-N-C- may be substituted with an alkyl having up to 7 carbon atoms or hydroxy groups,
or in which A is of the following formula (II):



(II)

wherein one or more of the carbon atoms selected from the group C_3, C_4, C_5, together with their substituents, may also be absent, and at least one substituent present in the range from B_1 to B_{10} is a C_{3-8}-cycloalkyl-(C_{0-9})-alkyl group, wherein both the C_{3-8} cycloalkyl group and the C_{0-9} alkyl group may comprise one or more double bonds and one or two carbon atoms of the cycloalkyl group may be replaced by nitrogen, oxygen or sulfur atoms, and wherein both the cycloalkyl group and the alkyl group may be substituted with hydroxy, halogen, amino, oxo groups with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, and the remaining substituents B_1 to B_{10} present are selected from the group which consists of hydrogen, hydroxy, halogen, amino groups, C_{1-26} alkyl residues, C_{1-26} alkoxy residues, C_{1-26}-alkoxy-C_{1-26}-alkyl residues or both substituents of a C atom together form an oxo group, wherein each C_{1-26} alkyl residue and each C_{1-26} alkoxy residue may be branched or unbranched and be saturated or unsaturated with one or more double bonds and may be substituted with hydroxy, amino, halogen and oxo groups,

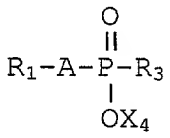
in which R_1 is selected from the group which consists of 5- and 6-membered heterocycles with at least one ring nitrogen atom or a polycyclic carbon with at least one of these heterocycles, wherein at least one of these nitrogen atoms belongs to a hydroxamic acid group or a hydroxamic acid ester group, and may be saturated or unsaturated with one or more double or triple bonds and may thus also be aromatic and may be substituted with hydroxy, halogen, amino, oxo groups and with branched or unbranched C_{1-9} alkyl groups and C_{2-9} alkenyl groups, wherein the C_{1-9} alkyl groups and C_{2-9} alkenyl groups may be saturated or unsaturated with one or more double or triple bonds and may be substituted with hydrogen, hydroxy, amino, halogen and oxo groups, wherein the nitrogen atom of the hydroxamic acid group or hydroxamic acid ester group is substituted with OR_5 and

R_5 is selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-9} alkyl, substituted and unsubstituted hydroxy-C_{1-9}-alkyl, substituted and unsubstituted C_{1-9} alkenyl, substituted and unsubstituted C_{1-9} alkynyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residue,

in which R_3 and R_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted acyl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, halogen, OX_3 and OX_4,

wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, substituted and unsubstituted C_{1-26} alkyl, substituted and unsubstituted hydroxy-C_{1-26}-alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted C_{1-26} alkenyl, substituted and unsubstituted C_{1-26} alkynyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residue, a silyl, a cation of an organic and inorganic base, in particular a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium and ammonium compounds derived from ethylenediamine or amino acids,
and the pharmaceutically acceptable salts, esters and amides thereof and salts of the esters.

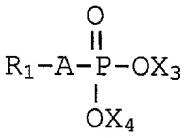
2. Compound according to claim 1, characterised in that the organophosphorus compounds are of the formula (III)



(III)

wherein R_3 is preferably hydrogen, methyl, ethyl, an amide residue and X_4 is selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl.

3. Compound according to claim 1, characterised in that the organophosphorus compounds are of the formula (IV)



(IV)

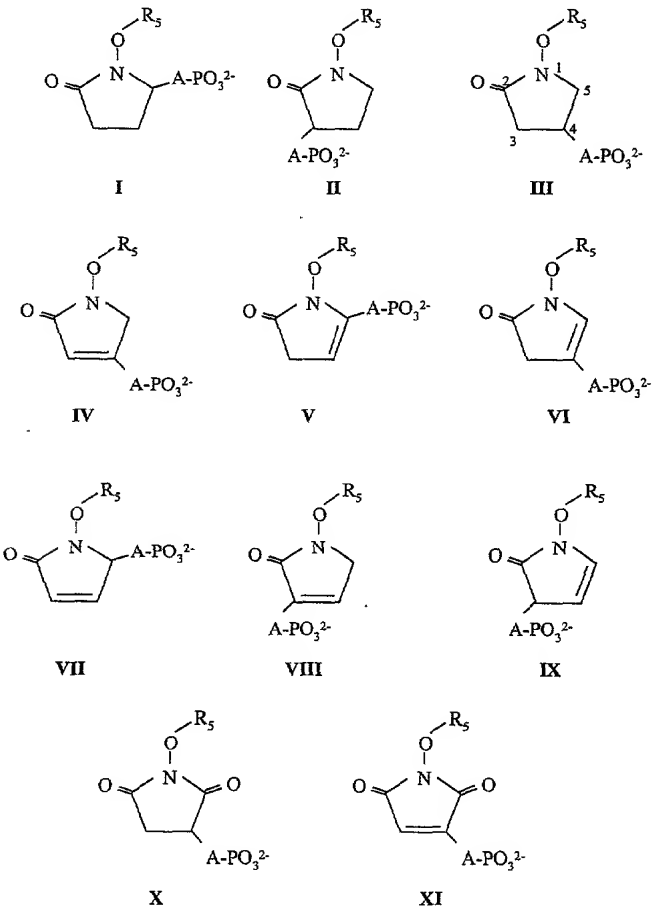
wherein X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, a (C_{1-3}) alkyl, a metal of main groups I, II or III of the periodic system, ammonium, substituted ammonium, or ammonium compounds derived from ethylenediamine or amino acids.

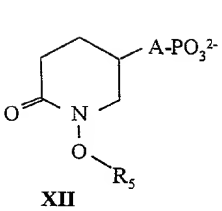
4. Compound according to claim 3, characterised in that X_3 and X_4 are identical or different and are selected from the group which consists of hydrogen, sodium, potassium, methyl, ethyl.

5. Compound according to one of the preceding claims, characterised in that A is selected from the group which consists of alkylene, alkenylene, hydroxyalkylene and oxoalkylene.

6. Compound according to claim 5, characterised in that A is selected such that three atoms are present between the nitrogen atom of the heterocyclic group and the phosphorus atom, wherein A is preferably a methylene, hydroxymethylene, ethylene, ethenylene or hydroxyethylene.

7. Compound according to one of claims 1 to 3, characterised in that the compound is selected from the group of compounds which consists of





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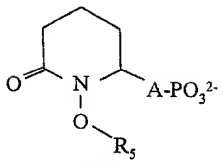

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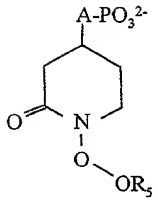

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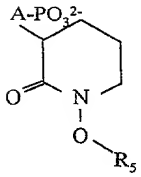

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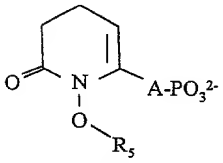

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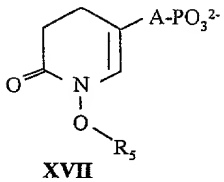

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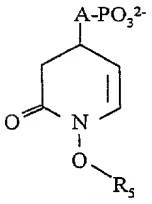

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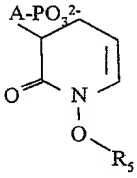

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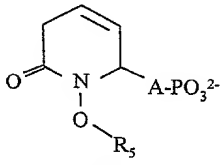

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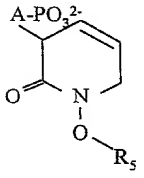

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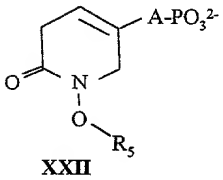

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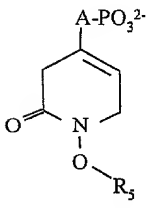

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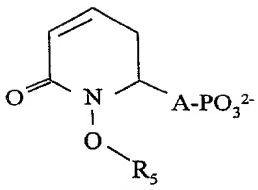

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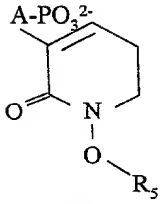

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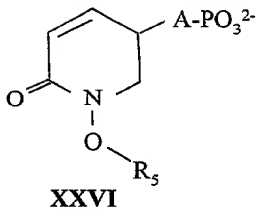

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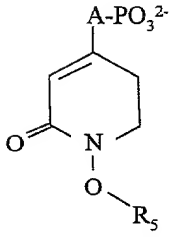

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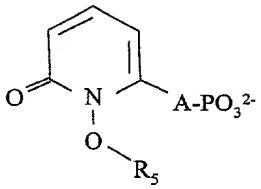

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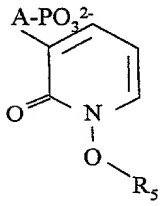

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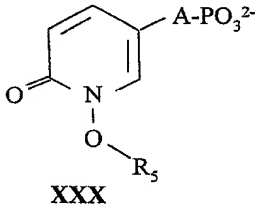

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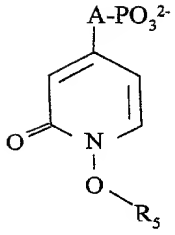

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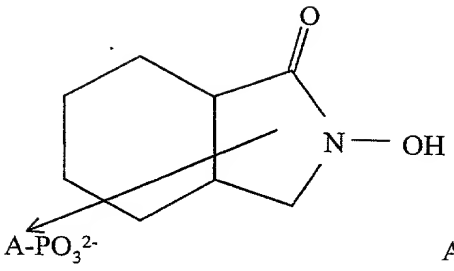

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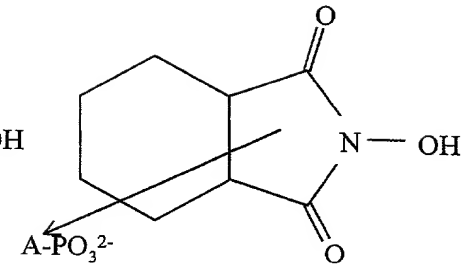

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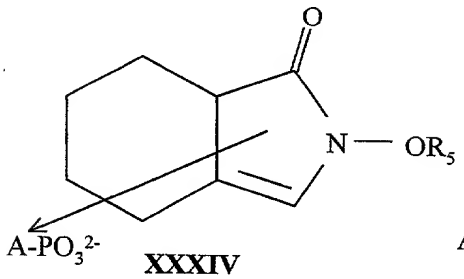

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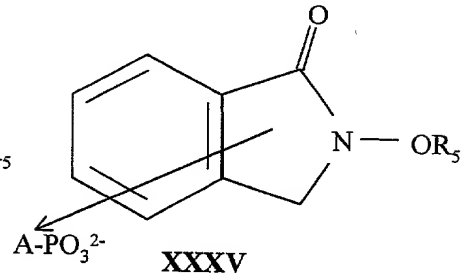

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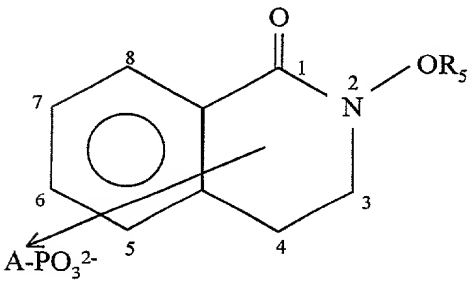

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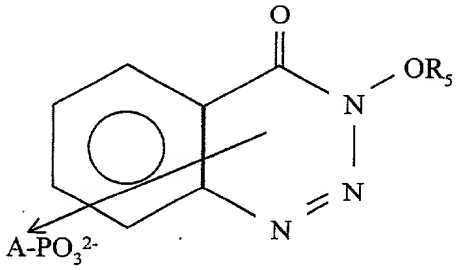

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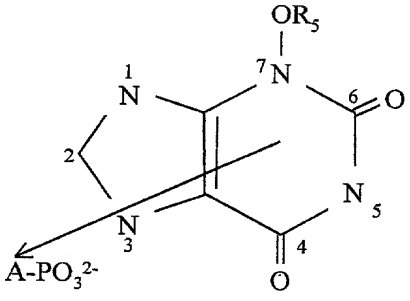

XXXVIII

and the corresponding phosphinic acid and phosphinoyl derivatives, wherein R_5 is defined as in claim 1.

8. Use of a compound according to one of claims 1 to 7 as a fungicide, bactericide or herbicide in plants.

9. Use according to one of claims 1 to 7 for the treatment of infections caused by bacteria, viruses, fungi or uni- or multicellular parasites.

10. Use according to claim 9 for the prevention and treatment of infections caused by unicellular parasites, namely the causative organisms of malaria, sleeping sickness, Chagas' disease, toxoplasmosis, amoebic dysentery, leishmaniases, trichomoniasis, pneumocystosis, balantidiasis, cryptosporidiosis, sarcocytosis, acanthamoebosis, naeglerosis, coccidiosis, giardiasis and lambliasis.

11. Pharmaceutical preparation for the therapeutic and prophylactic treatment of infectious processes, characterised in that the preparation contains an active content of at least one organophosphorus compound according to one of claims 1 to 7 together with a pharmaceutically acceptable excipient.

12. Pharmaceutical preparation according to claim 11, characterised in that the preparation contains another pharmaceutical active substance.

SUBSTITUTE SHEET (RULE 26)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER JOMAA-5 PCT

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ORGANOPHOSPHORUS COMPOUNDS AND USE THEREOF

the specification of which (check only one item below):

[ ] is attached hereto.

[ ] was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

[X] was filed as PCT international application

Number PCT/EP99/10274

on 22 DECEMBER 1999,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
GERMANY	198 59 426.7	22 DECEMBER 1998	[X] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO
			[ ] YES [ ] NO

US 15797 16478

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER JOMAA-5 PCT

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclose in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check One)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration numbers): KURT KELMAN, Registration No. 18,628
ALLISON C. COLLARD, Registration No. 22,532; WILLIAM C. COLLARD, Registration No. 38,411
EDWARD R. FREEDMAN, Registration No. 26,048; FREDERICK J. DORCHAK, Registration No. 29,298
ELIZABETH COLLARD RICHTER, Registration No. 35,103 REINE H. GLANZ, Registration No. 46,728

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2	FULL NAME OF INVENTOR	FAMILY NAME: JOMAA	FIRST GIVEN NAME: HASSAN	SECOND GIVEN NAME
0	RESIDENCE & CITIZENSHIP	CITY: GIESSEN DEX	STATE OR FOREIGN COUNTRY: GERMANY	COUNTRY OF CITIZENSHIP: GERMANY
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: FRANKFURTER STRASSE 50	CITY: D-35392 GIESSEN	STATE & ZIP CODE/COUNTRY: GERMANY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201

X Hassan Jomaa

DATE

06.06.2001

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